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(54) Title: OB PROTEIN RECEPTOR AND RELATED COMPOSITIONS AND METHODS		
(57) Abstract <p>The present invention relates to a novel class of protein receptors, herein denominated "OB protein receptors" or "OB receptors", which are thought to selectively bind OB protein. As such, the novel OB protein receptor family is provided, as well as novel members of such family. Also provided are nucleic acids, vectors and host cells containing such nucleic acids, related antisense nucleic acids, molecules which selectively bind to the OB protein receptor, and related compositions of matter, such as OB receptor protein/OB protein complexes and pharmaceutical compositions. In other aspects, the present invention relates to methods of using the above compositions, such as therapeutic and/or diagnostic methods, and methods for preparing OB receptor ligands.</p>		

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OB PROTEIN RECEPTOR AND RELATED COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

5 The present invention relates to OB protein receptors, related compositions and methods of making and using such receptors and related compositions.

BACKGROUND

10 Although the molecular basis for obesity is largely unknown, the identification of the "OB gene" and protein encoded ("OB protein") has shed some light on mechanisms the body uses to regulate body fat deposition. Zhang et al., Nature 372: 425-432 (1994); see
15 also, the Correction at Nature 374: 479 (1995). The OB protein is active in vivo in both *ob/ob* mutant mice (mice obese due to a defect in the production of the OB gene product) as well as in normal, wild type mice. The biological activity manifests itself in, among other
20 things, weight loss. See generally, Barinaga, "Obese" Protein Slims Mice, Science 269: 475-476 (1995). See PCT International Publication Number WO 96/05309, "Modulators of Body Weight, Corresponding Nucleic Acids and Proteins, and Diagnostic and Therapeutic Uses
25 Thereof," herein incorporated by reference.

 The other biological effects of OB protein are not well characterized. It is known, for instance, that in *ob/ob* mutant mice, administration of OB protein results in a decrease in serum insulin levels, and serum
30 glucose levels. It is also known that administration of OB protein results in a decrease in body fat. This was observed in both *ob/ob* mutant mice, as well as non-obese normal mice. Pellemounter et al., Science 269: 540-543 (1995); Halaas et al., Science 269: 543-546 (1995). See

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also, Campfield et al., Science 269: 546-549 (1995)
(Peripheral and central administration of microgram
doses of OB protein reduced food intake and body weight
of *ob/ob* and diet-induced obese mice but not in *db/db*
5 obese mice.) In none of these reports have toxicities
been observed, even at the highest doses.

Despite the promise of clinical application
of the OB protein, the mode of action of the OB protein
in vivo is not clearly elucidated, in part due to the
10 absence of information on the OB receptor. High affinity
binding of the OB protein has been detected in the rat
hypothalamus, reportedly indicating OB receptor loca-
tion. Stephens et al., Nature 377: 530-532 (1995). The
db/db mouse displays the identical phenotype as the
15 *ob/ob* mouse, i.e., extreme obesity and Type II diabetes;
this phenotype is thought to be due to a defective OB
receptor, particularly since *db/db* mice fail to respond
to OB protein administration. See Stephens et al.,
supra.

20 Identification of the OB protein receptor is
key in determining the pathway of signal transduction.
Moreover, identification of the OB protein receptor
would provide powerful application in diagnostic uses,
for example, to determine if individuals would benefit
25 from OB protein therapy. Furthermore, the OB receptor
could be a key component in an assay for determining
additional molecules which bind to the receptor and
result in desired biological activity. Further, such
soluble receptor could enhance or alter the effective-
30 ness of OB protein (or analog or derivative thereof).

SUMMARY OF THE INVENTION

The present invention relates to a novel class
of protein receptors, herein denominated "OB protein
35 receptors" or "OB receptors", which are thought to
selectively bind OB protein. As such, the novel OB

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receptor family is provided, as well as novel members of such family. Also provided are nucleic acids, vectors and host cells containing such nucleic acids, related antisense nucleic acids, molecules which selectively
5 bind to the OB protein receptor, and related compositions of matter, such as OB receptor protein/OB protein complexes. In other aspects, the present invention relates to methods of using the above compositions, such as therapeutic and/or diagnostic methods, and methods
10 for preparing OB receptor ligands.

DETAILED DESCRIPTION

A novel family of OB receptors is provided. This novel family resulted from identification of a PCR
15 fragment isolated from a human liver cell cDNA library. The original PCR fragment, from which primers were isolated, contained a "WSXWS" motif, common to cytokine receptors. As illustrated by the working examples below, using this fragment four members of this OB
20 protein receptor family have been identified. These members, herein designated as "A", "B", and "C", and "D" are identical at amino acid position 1-891 (using the numbering of Seq. ID No. 1), but diverge at position 892 through the C-terminus. They vary in length at the
25 C-terminus beyond amino acid 891, and the different forms appear to have different tissue distribution.

Using hydrophobicity analysis, the leader sequence is likely to comprise amino acids (Seq. ID. No. 1) 1-21, 1-22, or 1-28. The first amino acid of the
30 mature protein is likely to be 22 (F), 23 (N) or 29 (T). Most likely, based on analysis of eucaryotic cell expression (CHO cell expression see Example 8, infra), the first amino acid of the mature protein is 22(F). The beginning of the transmembrane domain appears to be
35 located at position 840 (A) or 842 (L). The end of the transmembrane domain appears to be located at position

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862 (I), 863 (S) or 864 (H). Thus, based on predictions from hydrophobicity analysis, for OB protein binding, at a minimum what is needed is the extracellular domain of the mature protein, amino acids 22, 23 or 29 through amino acids 839 (D) or 841 (G). Therefore, the present class of OB receptor proteins includes those having amino acids (according to Seq. ID No. 1):

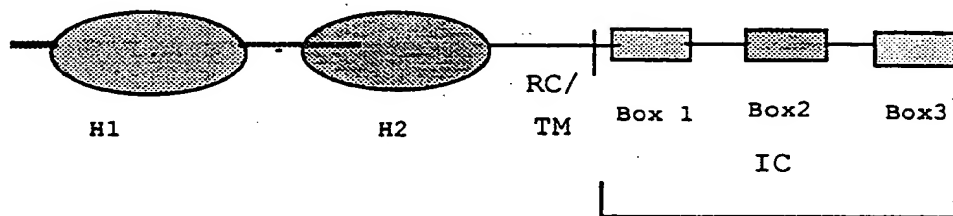
- (a) 1-896;
- (b) 22-896;
- 10 (c) 23-896;
- (d) 29-896;
- (e) 1-839;
- (f) 22-839;
- (h) 1-841;
- 15 (i) 22-841;
- (j) 23-841;
- (k) 29-841;
- (l) 1-891;
- (m) 22-891;
- 20 (n) 23-891;
- (o) 29-891;
- (p) the amino acids of subparts (l) through (o) having the C-terminal amino acids selected from among:
- 25 (i) OB receptor B (Seq. ID No. 3) positions 892-904;
- (ii) OB receptor C (Seq. ID No. 5) positions 892- 958; and,
- (iii) OB receptor D (Seq. ID No. 7) positions 892-1165;
- 30 (q) amino acids of subparts b, c, d, f, g, i, j, k, m, n, o, and any of (p) lacking a leader sequence, which have an N-terminal methionyl residue.

35 Also provided herein is what is thought to be a human splice variant of a soluble OB receptor. This

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splice variant includes the extracellular domain at least up to amino acid 798 (of Seq. ID No. 1, for example) and has a unique 6 amino acid C-terminus at positions 799-804: G K F T I L.

5 The functional domains of the OB receptor may be predicted using the information contained in Bazan et al., PNAS-USA 87: 6934-6938 (1990) (incorporated herein by reference). For the present OB receptor, there are two hematopoietin domains, a random coil region, the
10 transmembrane domain, and the intracellular domain. The overall geography may be illustrated as follows:



Using the information provided by Bazan,
15 supra, the domains may be predicted, with essentially an error of approximately plus or minus three base pairs (as applied to all amino acid location specified for purposes of identifying the Bazan predicted domains). The precise locations may be determined empirically by
20 methods known in the art, such as preparing and expressing modified recombinant DNAs. The structural characteristics are thought to be important for maintaining the structural integrity of the molecule, and therefore, to the extent that such structure is
25 important for function, for functional characteristics as well.

The hematopoietin domains (H1 and H2) are thought to have two fibronectin type 3 repeats each, one set of paired cysteine residues each (thought to form a
30 disulfide bridge), and one "WSXWS box" (referring to the

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single letter amino acid abbreviation, with "X" being any amino acid). The fibrinectin type 3 domains may be identified by location of a double proline ("PP"), which marks the beginning of the second fibronectin type 3 repeat; the actual beginning of such second fibronectin type 3 repeat is likely to begin about 3 amino acids upstream of that double proline.

The first hematopoietin domain is likely to begin at amino acid 123 (using the numbering according to Seq. ID No. 1, for example), which is an isoleucine residue (I). The last amino acid of the hematopoietin domain is likely to be amino acid 339, which is a lysine (K) residue. The two fibronectin type 3 repeats are likely to be located at (about) amino acids 123 through 235 and 236 through 339. There is a single pair of cysteine residues which likely form a disulfide bridge, located at position 131 and position 142. The "WSXWS box" is located at position 319 through 323.

The second hematopoietin domain is likely to begin at position 428, which is an isoleucine (I) and end at position 642 which is a glycine (G). The paired fibronectin type 3 repeats are located at about position 428 through position 535 and about position 536 through about position 642. One pair of cysteines is located at position 436 and position 447, and the second pair is located at position 473 and 488. The "WSXWS box" is located at position 622-626.

Between the first and the second hematopoietin domain (amino acids 339-428, approximately) is a region of unknown functional significance.

The random coil domain ("RC" between the H2 and the transmembrane domain, "TM") is likely to begin at the amino acid following the end of the second hematopoietin domain, and is likely to end at the beginning of the transmembrane domain. This is likely to be from about amino acid 642 through amino acid 839

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or 841 (with the transmembrane domain beginning at position 840 (A) or 842 (L)). The intracellular domain ("IC") is likely to begin at position 861 (L), 862 (I), 863 (S) or 864 (H).

5 The intracellular domain ("IC") contains three regions, or "boxes," thought to participate in signal transduction (two "JAK" boxes and a single "STAT" box, "Box 1", "Box 2", and "Box 3"). With respect to the numbering of the amino acid positions of the "D" form of
10 the OB receptor (Seq. ID No.7, below), box 1 is located at amino acid 871 (F) through 878 (P). Box 2 is located at approximately amino acid number 921 (I) through 931 (K). Box 3 on the "D" form is located at approximately position 1141 through 1144 (amino acids YMPQ, as
15 the "STAT" box is typically a conserved region of "YXXQ" wherein "X" designates any amino acid). The intracellular domain is thought to be responsible for signal transduction. One possible mode of action is via phosphorylation of various residues. See Ihle et al.,
20 Cell 84: 331-334 (1996) (Review article, herein incorporated by reference.)

One possible mode of action is that upon ligand binding (here, OB protein binding), the OB receptor dimerizes with another receptor. A kinase
25 ("JAK") binds to box 1, and becomes phosphorylated. (The JAK may already be bound prior to dimerization.) Also, "STATs" bind to box 3 and become phosphorylated on a specific tyrosine. It is thought that this phosphorylation results, probably indirectly, in DNA
30 binding protein production, which results in altered DNA transcription, and therefore altered expression. As seen below in Example 6, one measurement of the capability of an OB receptor to transduce signal is the degree of phosphorylation of JAK/STAT molecules.

35 The C-terminus region is intracellular (of cell-bound OB receptor). The differences in the C-

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terminus among members of the present OB receptor family may result in differences in signal transduction among the species. Thus, the present OB receptors include at least the extracellular domain which is important for OB protein ligand binding. Nucleic acids encoding the present OB receptors, vectors, and host cells are also provided for herein.

The extracellular domain may be modified and still retain the function of ligand binding, particularly by one or more of the following modifications: (a) the random coil domain (as indicated above, occurring downstream of the second hematopoietic domain through the beginning of the transmembrane domain) may be deleted (this may be approximately positions 642 through 839 or 841); (b) the "WSXWS" box may be modified by (i) substitution of the first serine with another amino acid, particularly conserved in terms of hydrophobicity and/or charge, such as a glycine; (ii) the last serine may be substituted with another amino acid, such as a threonine; (iii) the first tryptophan may be substituted with another amino acid, for example, a tyrosine.

Human genomic DNA encoding OB receptor protein is also provided herein. The genomic DNA has been localized to human chromosome 1P31, which is believed to correspond to mouse chromosome 4, the location of the mouse *db* locus.

Tissue distribution analysis demonstrates the presence of OB receptor nucleic acids is fairly ubiquitous, and particularly noted in the liver. It is also observed in the ovary, and heart; and, to a lesser extent, in small intestine, lung, skeletal muscle, kidney, and, to an even lesser extent, spleen, thymus, prostate, testes, placenta and pancreas (Example 2, below). There may also be one or more forms of the OB receptor present in serum, such as soluble OB receptor,

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which may be complexed to one or more forms of the OB protein.

Amino Acid Sequences and Compositions

5 According to the present invention, novel OB protein receptors and DNA sequences coding for all or part of such OB receptors are provided. The present invention provides purified and isolated polypeptide products having part or all of the primary structural
10 conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vitro biological activity) and physical properties (e.g., molecular weight) of naturally-occurring mammalian OB receptor
15 including allelic variants thereof. The term "purified and isolated" herein means substantially free of unwanted substances so that the present polypeptides are useful for an intended purpose. For example, one may have a recombinant human OB receptor substantially free
20 of human proteins or pathological agents. These polypeptides are also characterized by being a product of mammalian cells, or the product of chemical synthetic procedures or of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast, higher plant,
25 insect and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis. The products of expression in typical yeast (e.g., Saccharomyces cerevisiae), insect, or procaryote (e.g., E. coli) host cells are free of association with
30 any mammalian proteins. The products of expression in vertebrate (e.g., non-human mammalian (e.g. COS or CHO) and avian) cells are free of association with any human proteins. Depending upon the host employed, and other factors, polypeptides of the invention may be
35 glycosylated with mammalian or other eucaryotic carbohydrates or may be non-glycosylated. One may modify

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the nucleic acid so that glycosylation sites are included in the resultant polypeptide. One may choose to partially or fully deglycosylate a glycosylated polypeptide. Polypeptides of the invention may also
5 include an initial methionine amino acid residue (at position -1 with respect to the first amino acid residue of the mature polypeptide).

In addition to naturally-occurring allelic forms of OB receptor, the present invention also
10 embraces other OB receptor products such as polypeptide analogs of OB receptor and fragments of OB receptor. Following the procedures of the above noted published application by Alton et al. (WO 83/04053), one can readily design and manufacture genes coding for
15 microbial expression of polypeptides having primary conformations which differ from that herein specified for in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions). Alternately, modifications of
20 cDNA and genomic genes may be readily accomplished by well-known site-directed mutagenesis techniques and employed to generate analogs and derivatives of OB receptor. Such products would share at least one of the biological properties of mammalian OB receptor but may
25 differ in others. As examples, projected products of the invention include those which are foreshortened by e.g., deletions; or those which are more stable to hydrolysis (and, therefore, may have more pronounced or longer lasting effects than naturally-occurring); or
30 which have been altered to delete one or more potential sites for glycosylation (which may result in higher activities for yeast-produced products); or which have one or more cysteine residues deleted or replaced by, e.g., alanine or serine residues and are potentially
35 more easily isolated in active form from microbial systems; or which have one or more tyrosine residues

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replaced by phenylalanine; or have an altered lysine composition (such as those prepared for purposes of derivatization). Included are those polypeptides with amino acid substitutions which are "conservative"

5 according to acidity, charge, hydrophobicity, polarity, size or any other characteristic known to those skilled in the art. See generally, Creighton, Proteins, W.H. Freeman and Company, N.Y., (1984) 498 pp. plus index, passim. One may make changes in selected amino acids so

10 long as such changes preserve the overall folding or activity of the protein, (see Table 1, below). Small amino terminal extensions, such as an amino-terminal methionine residue, a small linker peptide of up to about 20-25 residues, or a small extension that facili-

15 tates purification, such as a poly-histidine tract, an antigenic epitope or a binding domain, may also be present. See, in general Ford et al., Protein Expression and Purification 2: 95-107, 1991, which is herein incorporated by reference.

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Table 1
Conservative Amino Acid Substitutions

Basic:	arginine lysine histidine
Acidic:	glutamic acid aspartic acid
Polar:	glutamine asparagine
Hydrophobic:	leucine isoleucine valine
Aromatic:	phenylalanine tryptophan tyrosine
Small:	glycine alanine serine threonine methionine

5 Also comprehended are polypeptide fragments duplicating only a part of the continuous amino acid sequence or secondary conformations within OB receptor, which fragments may possess one activity of mammalian (particularly human) OB receptor (e.g., immunological
10 activity) and not others (e.g., OB protein binding activity).

Of applicability to OB receptor fragments and polypeptide analogs of the invention are reports of the immunological activity of synthetic peptides which
15 substantially duplicate the amino acid sequence extant in naturally-occurring proteins, glycoproteins and nucleoproteins. More specifically, relatively low

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molecular weight polypeptides have been shown to participate in immune reactions which are similar in duration and extent to the immune reactions of physiologically significant proteins such as viral antigens, polypeptide hormones, and the like. Included among the immune reactions of such polypeptides is the provocation of the formation of specific antibodies in immunologically active animals. See, e.g., Lerner et al., Cell 23: 309-310 (1891); Ross et al., Nature 294: 654-656 (1891); Walter et al., PNAS-USA 77: 5197-5200 (1980); Lerner et al., PNAS-USA, 78: 3403-3407 (1891); Walter et al., PNAS-USA 78: 4882-4886 (1891); Wong et al., PNAS-USA 79: 5322-5326 (1982); Baron et al., Cell 28: 395-404 (1982); Dressman et al., Nature 295: 185-160 (1982); and Lerner, Scientific American 248: 66-74 (1983). See, also, Kaiser et al. Science 223: 249-255 (1984) relating to biological and immunological activities of synthetic peptides which approximately share secondary structures of peptide hormones but may not share their primary structural conformation. The present invention also includes that class of polypeptides coded for by portions of the DNA complementary to the protein-coding strand of the human cDNA or genomic DNA sequences of OB receptor i.e., "complementary inverted proteins" as described by Tramontano et al. Nucleic Acid Res. 12: 5049-5059 (1984). Polypeptides or analogs thereof may also contain one or more amino acid analogs, such as peptidomimetics.

Thus, the present class of OB receptor proteins includes those having amino acids (according to Seq. ID No. 1):

- (a) 1-896;
- (b) 22-896;
- (c) 23-896;
- (d) 29-896
- (e) 1-839;

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- (f) 22-839;
(g) 29-839;
(h) 1-841;
(i) 22-841;
5 (j) 23-841;
(k) 29-841;
(l) 1-891;
(m) 22-891;
(n) 23-891;
10 (o) 29-891;
(p) the amino acids of subparts (l) through (o) having the C-terminal amino acid sequence beginning at position 892 of OB receptor B (Seq. ID No. 3) or C (Seq. ID. No. 5);
15 (q) amino acids of subparts b, c, d, f, g, i, j, k, m, n, o, and any of (p) lacking a leader sequence, which have an N-terminal methionyl residue.
- Also provided is a longer form of an OB receptor protein, herein denominated the "D" form, which
20 has an amino acid sequence selected from among (according to Seq. ID No. 7):
- (a) amino acids 1-1165;
(b) amino acids 22-1165;
(c) amino acids 23-1165;
25 (d) amino acids 29-1165;
(e) amino acids of subparts (b), (c) or (d) having an N-terminal methionyl residue.
- As set forth above, one may prepare soluble receptor by elimination of the transmembrane and intra-
30 cellular regions. Examples of soluble receptors include those set forth in Seq. ID Nos. 10 and 13. What is thought to be a native, secreted form of a soluble human OB receptor is also provided herein. This form of OB receptor protein has an amino acid sequence selected
35 from among (according to Seq. ID No. 13):
- (a) amino acids 1-804;

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- (b) amino acids 22-804;
 - (c) amino acids 23-804;
 - (d) amino acids 29-804; and,
 - (e) amino acids of subparts (b), (c) or
- 5 (d) having an N-terminal methionyl residue.

In addition, since the C-terminus region of the above polypeptides diverges at position 892 (with respect to Seq. ID Nos. 1, 3, 5, 7 and 13) one may desire to prepare only the polypeptides which are

10 divergent:

- (a) those having only amino acids 892-896 of Seq. ID No. 1;
 - (b) those having only amino acids 892-904 of Seq. ID No. 3;
 - 15 (c) those having only amino acids 892-958 of Seq. ID No. 5;
 - (d) those having only amino acids 892-1165 of Seq. ID No. 7; and,
 - (e) those having only amino acids 799-804
- 20 of Seq. ID No. 13.

The above polypeptides which have an extracellular domain may be modified, as indicated above, and still retain the function of ligand binding. Such modification may include one or more of the

25 following:

- (a) the random coil domain (as indicated above, occurring downstream of the second hematopoietic domain through the beginning of the transmembrane domain) may be deleted (this may be approximately
- 30 positions 642 through 839 or 841);
- (b) the "WSXWS" box may be modified by
 - (i) substitution of the first serine with another amino acid, particularly conserved in terms of hydrophobicity and/or charge, such as a glycine; (ii) the last serine
- 35 may be substituted with another amino acid, such as a threonine; (iii) the first tryptophan may be

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substituted with another amino acid, for example, a tyrosine.

Thus, the present polypeptides include (according to the numbering of Seq. ID No. 7):

- 5 (a) 1-896;
(b) 22-896;
(c) 23-896;
(d) 29-896
(e) 1-839;
10 (f) 22-839;
(g) 29-839;
(h) 1-841;
(i) 22-841;
(j) 23-841;
15 (k) 29-841;
(l) 1-891;
(m) 22-891;
(n) 23-891;
(o) 29-891;
20 (p) the amino acids of subparts (l) through (o) having the C-terminal amino acids selected from the C-terminal amino acids of OB receptor B (Seq. ID No. 3), C (Seq. ID. No. 5) and D (Seq ID No. 7);
(q) the amino acids (according to Seq. ID
25 No. 13) selected from the group consisting of 22-804; 23-804 and 29-804;
(r) amino acids of subparts b, c, d, f, g, i, j, k, m, n, o, any of (p) lacking a leader sequence, and (q) which have an N-terminal methionyl
30 residue; and
(s) amino acids of subparts (a) through (r) which above having at least one of the following modifications:
(i) for amino acids of subparts (a)
35 through (p) and those of subpart (r) which are not amino acids according to subpart (q), deletion of (or

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substitution of amino acid(s) or other modifications of)
a random coil domain sequence selected from

(a) 640 through 839 (using
the numbering according to Seq. ID No. 1);

5

(b) 641 through 839;

(c) 642 through 839;

(d) 640 through 841;

(e) 641 through 841; and

(f) 642 through 841;

10

(ii) for amino acids of subpart (q)

and those of subpart (r) which contain the sequence of
subpart (q); deletion of of (or substitution of amino
acid(s) or other modifications of) a random coil domain
sequence selected from among:

15

(a) 640 through 804;

(b) 641 through 804; and,

(c) 642 through 804;

and,

(iii) modification of a "WSXWS"

20

sequence which is

(a) substitution of the first
serine with another amino acid, particularly conserved
in terms of hydrophobicity and/or charge, such as a
glycine;

25

(b) substitution of the last
serine with another amino acid, such as a threonine;
and

(c) substitution of the first
tryptophan with another amino acid, for example, a
tyrosine.

30

One may modify the OB receptor to create a
fusion molecule with other peptide sequence. For
example, if one desired to "tag" the OB receptor with an
immunogenic peptide, one could construct a DNA which
would result in such fusion protein. The tag may be at
the N-terminus. Also, since it is apparent that the

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C-terminus is not necessary for ligand binding activity, one may chemically modify the C-terminus of, for example, a soluble OB receptor. One may desire, for example, a preparation whereby one or more polymer
5 molecules such as polyethylene glycol molecules are attached. Thus, another aspect of the present invention is chemically modified OB receptor protein (also further described infra).

An example of such "tag" is provided herein
10 using the C-terminus of a recombinant soluble OB receptor. Seq. ID No. 12 provides a "FLAG-tag" version of such soluble OB receptor (the nucleic acid sequence is provided, which may be transcribed to prepare the polypeptide). Such "FLAG-tag" may also be attached to
15 the N-terminus or other region of an OB receptor protein. This type of "tagging" is useful to bind the protein using reagents, such as antibodies, which are selective for such tag. Such binding may be for detection of the location or amount of protein, or for
20 protein capturing processes where, for example, an affinity column is used to bind the tag, and thus the desired protein. Other types of detectable labels, such as radioisotopes, light-emitting (e.g., fluorescent or phosphorescent compounds), enzymatically cleavable,
25 detectable antibody (or modification thereof), or other substances may be used for such labelling of the present proteins. Detecting protein via use of the labels may be useful for identifying the presence or amount of OB receptor protein or a compound containing such protein
30 (e.g., OB protein complexed to OB receptor). Moreover, such labelled protein may be useful for distinguishing exogenous OB receptor protein from the endogenous form.

Nucleic Acids

Novel nucleic acid sequences of the invention include sequences useful in securing expression in procaryotic or eucaryotic host cells of polypeptide products having at least a part of the primary structural conformation and one or more of the biological properties of recombinant human OB receptor. The nucleic acids may be purified and isolated, so that the desired coding region is useful to produce the present polypeptides, for example, or for diagnostic purposes, as described more fully below. DNA sequences of the invention specifically comprise: (a) any of the DNA sequences set forth in Seq. ID No. 2, 4, 6, 8, 9, 11, 12, and 14 (and complementary strands); (b) a DNA sequence which hybridizes (under hybridization conditions disclosed in the cDNA library screening section below, using the 300 bp PCR fragment as described to selectively hybridize to a cDNA encoding an OB receptor protein in a human liver cDNA library, or equivalent conditions or more stringent conditions) to the DNA sequence in subpart (a) or to fragments thereof; and (c) a DNA sequence which, but for the degeneracy of the genetic code, would hybridize to the DNA sequence in subpart (a). Specifically comprehended in parts (b) and (c) are genomic DNA sequences encoding allelic variant forms of human OB receptor and/or encoding OB receptor from other mammalian species, and manufactured DNA sequences encoding OB receptor, fragments of OB receptor, and analogs of OB receptor which DNA sequences may incorporate codons facilitating transcription and translation of messenger RNA in microbial hosts. Such manufactured sequences may readily be constructed according to the methods of Alton et al., PCT published application WO 83/04053.

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Genomic DNA, such as that of Seq. ID No. 9, encoding the present OB receptors may contain additional non-coding bases, or introns, and such genomic DNAs are obtainable by hybridizing all or part of the cDNA, 5 illustrated in Seq. ID Nos. 2, 4, 6, 8, 11, and 14 to a genomic DNA source, such as a human genomic DNA library. Such genomic DNA will encode functional OB receptor polypeptide; however, use of the cDNAs may be more practicable in that, since only the coding region is 10 involved, recombinant manipulation is facilitated. The intron/exon location of genomic DNA is set forth in Seq. ID No. 9, infra.

Nucleic acid sequences include the incorporation of codons which enhance expression by 15 selected nonmammalian hosts; the provision of sites for cleavage by restriction endonuclease enzymes; and the provision of additional initial, terminal or intermediate DNA sequences which facilitate construction of cloning and/or expression vectors.

20 The present invention also provides DNA sequences coding for polypeptide analogs or derivatives of OB receptor which differ from naturally-occurring forms in terms as described above. The leader sequence DNA may be substituted with another leader sequence for 25 ease in expression or for other purposes.

Also, one may prepare antisense nucleic acids against the present DNAs. Such antisense nucleic acids may be useful in modulating the effects of OB receptor protein in vivo. For example, one may prepare an 30 antisense nucleic acid which effectively disables the ability of a cell to produce OB receptor by binding to the nucleic acid which encodes such OB receptor.

DNA sequences of the invention are also suitable materials for use as labeled probes in 35 isolating human genomic DNA encoding OB receptor, as mentioned above, and related proteins as well as cDNA

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and genomic DNA sequences of other mammalian species. DNA sequences may also be useful in various alternative methods of protein synthesis (e.g., in insect cells) or, as described infra, in genetic therapy in humans and other mammals. DNA sequences of the invention are expected to be useful in developing transgenic mammalian species which may serve as eucaryotic "hosts" for production of OB receptor and OB receptor products in quantity. See, generally, Palmiter et al., Science 222: 809-814 (1983).

Vectors and Host Cells

According to another aspect of the present invention, the DNA sequences described herein which encode OB receptor polypeptides are valuable for the information which they provide concerning the amino acid sequence of the mammalian protein which have heretofore been unavailable. Put another way, DNA sequences provided by the invention are useful in generating new and useful viral and circular plasmid DNA vectors, new and useful transformed and transfected procaryotic and eucaryotic host cells (including bacterial cells, yeast cells, insect cells, and mammalian cells grown in culture), and new and useful methods for cultured growth of such host cells capable of expression of OB receptor and its related products.

The DNA provided herein (or corresponding RNAs) may also be used for gene therapy for, example, treatment of conditions characterized by the overexpression of OB protein, such as anorexia or cachexia. Alternatively, gene therapy may be used in cases where increased sensitivity to OB protein is desired, such as in cases where an individual has a condition characterized by OB protein receptors defective in ability to bind or retain the binding of OB protein. Currently, vectors suitable for gene therapy

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(such as retroviral or adenoviral vectors modified for gene therapy purposes and of purity and pharmaceutical acceptability) may be administered for delivery into the lung, for example. Such vectors may incorporate nucleic acid encoding the present polypeptides for expression in a desired location. Gene therapy may involve more than one gene for a desired protein or different desired proteins.

Alternatively, one may use no vector so as to facilitate relatively stable presence in the host. For example, homologous recombination of a DNA as provided herein or of a suitable transcription or translation control region may facilitate integration into or expression from a host genome. (This may be performed for production purposes as well, e.g., U.S. Patent No. 5,272,071 and WO 91/09955.) The nucleic acid may be placed within a pharmaceutically acceptable carrier to facilitate cellular uptake, such as a lipid solution carrier (e.g., a charged lipid), a liposome, or polypeptide carrier (e.g., polylysine). A review article on gene therapy is Verma, Scientific American, November 1990, pages 68-84 which is herein incorporated by reference.

Thus, the present invention provides for a population of cells expressing an OB receptor of the present OB receptor family. Such cells are suitable for transplantation or implantation into an individual for therapeutic purposes. For example, one may prepare a population of cells to overexpress OB receptor (such as one identified in the Sequence ID's or otherwise denoted herein), or to express a desired form of OB receptor, such as one which is particularly sensitive to OB protein (i.e., a form which has a desired capacity for signal transduction). One may then implant such cells into an individual to increase that individual's sensitivity to OB protein. Such cells may, for example,

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be liver cells, bone marrow cells, or cells derived from umbilical cord. Alternatively, one may wish to use overexpressing circulating cells such as blood progenitor cells, T cells or other blood cells. For
5 humans, human cells may be used. Cells may be in the form of tissue. Such cells may be cultured prior to transplantation or implantation. Such OB receptor overexpression, or expression of particularly sensitive forms of OB receptor may be accomplished by, for
10 example, altering the regulatory mechanism for expression of OB receptor, such as using homologous recombination techniques as described supra. Thus, provided is a population of host cells modified so that expression of endogenous OB receptor DNA is enhanced.

15 The cells to be transferred to the recipient may be cultured using one or more factors affecting the growth or proliferation of such cells if appropriate. Hematopoietic factors may be used in culturing hematopoietic cells. Such factors include G-CSF, EPO,
20 MGDF, SCF, Flt-3 ligand, interleukins (e.g., IL1-IL13), GM-CSF, LIF, and analogs and derivatives thereof as available to one skilled in the art.

Nerve cells, such as neurons or glia, may also be used, and these may be cultured with neurotrophic
25 factors such as BDNF, CNTF, GDNF, NT3, or others.

There may be a co-gene therapy involving the transplantation of cells expressing more than one desired protein. For example, cells expressing OB
30 receptor protein may be used in conjunction, simultaneously or in seriatim with cells expressing OB protein.

For gene therapy dosages, one will generally use between one copy and several thousand copies of the present nucleic acid per cell, depending on the vector,
35 the expression system, the age, weight and condition of the recipient and other factors which will be apparent

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to those skilled in the art. The cellular delivery of such protein may be designed to last for a selected period of time, such as a period of days, weeks, months or years. At the end of the effective time period, the recipient of such transformed cells may receive another "dose" (e.g., transplantation of cells). Cells may be selected for their lifespan, their time period of expression of the desired protein, or their ability to be reisolated from an individual (i.e., for blood cells, leukaphoresis may be used to retrieve transformed cells using markers present on the cell surface). Vectors may be similarly designed using, for example, viruses which have a known period of expression of DNAs contained therein.

The desired cells or vectors may be stored using techniques, such as freezing, available to those in the art.

Thus, the present invention also contemplates a method for administering OB receptor protein to an individual, wherein the source of said OB receptor protein is selected from (i) a population of cells expressing OB receptor protein and (ii) a population of vectors expressing OB receptor protein. Said OB receptor protein may be selected from among those described herein. Said vectors may be virus vectors capable of infecting human cells. Said cells may be selected from among tissue or individual cells. Said individual cells may be selected from among adipocytes, fibroblasts, bone marrow cells, peripheral blood progenitor cells, red blood cells, and white blood cells, including T cells and nerve cells. Said population of cells or vectors may be co-administered with a population of cells or vectors which express OB protein or another desired protein. Said cells or vectors may be stored for use in an individual. Storage may be by freezing

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Complexes

In addition to the OB receptor protein as described herein, one may prepare complexes of OB
5 receptor protein and OB protein, analog or derivative.

The OB protein may be selected from those described in PCT publication WO 96/05309, above and hereby incorporated by reference in its entirety. Figure 3 of that publication (Seq. ID No. 4, as cited
10 therein) depicts the full deduced amino acid sequence derived for the human OB gene. The amino acids are numbered from 1 to 167. A signal sequence cleavage site is located after amino acid 21 (Ala) so that the mature protein extends from amino acid 22 (Val) to amino acid
15 167 (Cys). For the present disclosure, a different numbering is used herein, where the amino acid position 1 is the Valine residue which is at the beginning of the mature protein.

Generally, the OB protein for use will be
20 capable of complexing to the OB protein receptor selected. Thus, one may empirically test the binding capability (to all or part of the extracellular domain of the OB receptor as indicated above) to determine which OB protein forms may be used. Generally,
25 modifications generally applicable as indicated above for OB receptor protein may also be applied here, and that disclosure is incorporated by reference here. As set forth in WO 96 05309, OB protein in its native form, or fragments (such as enzyme cleavage products) or other
30 truncated forms, analogs, and derivatives all retain biological activity. Such forms may be used so long as the form binds to at least a portion of the extracellular domain of the present OB receptor proteins.

35 An effective amount of an OB protein, analog or derivative thereof may be selected from among

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according to the amino acid sequence as presented in PCT WO 96/05309, Figure 3 numbered so that the first amino acid of the mature protein is number 1:

- 5 (a) the amino acid sequence 1-146,
optionally lacking a glutamyl residue at position 28,
and further optionally having a methionyl residue at the N-terminus;

- (b) an amino acid sequence of subpart
10 (a) having a different amino acid substituted in one or
more of the following positions: 4, 8, 32, 33, 35, 48,
50, 53, 60, 64, 66, 67, 68, 71, 74, 77, 78, 89, 97,
100, 102, 105, 106, 107, 108, 111, 112, 118, 136, 138,
142, and 145;

- (c) a truncated OB protein analog
15 selected from among: (using the numbering of subpart (a)
above):

- (i) amino acids 98-146
(ii) amino acids 1-32
(iii) amino acids 1-35
20 (iv) amino acids 40-116
(v) amino acids 1-99 and 112-146
(vi) amino acids 1-99 and 112-146
having one or more of amino acids 100-111
sequentially placed between amino acids 99 and 112;
25 and,

- (vii) the truncated OB analog of
subpart (i) having one or more of amino acids 100,
102, 105, 106, 107, 108, 111, 112, 118, 136, 138,
142, and 145 substituted with another amino acid;
30 (viii) the truncated analog of subpart
(ii) having one or more of amino acids 4, 8 and 32
substituted with another amino acid;

- (ix) the truncated analog of subpart
(iv) having one or more of amino acids 50, 53, 60,
35 64, 66, 67, 68, 71, 74, 77, 78, 89, 97, 100, 102,

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105, 106, 107, 108, 111 and 112 replaced with another amino acid;

5 (x) the truncated analog of subpart (v) having one or more of amino acids 4, 8, 32, 33, 35, 48, 50, 53, 60, 64, 66, 67, 68, 71, 74, 77, 78, 89, 97, 112, 118, 136, 138, 142, and 145 replaced with another amino acid;

10 (xi) the truncated analog of subpart (vi) having one or more of amino acids 4, 8, 32, 33, 35, 48, 50, 53, 60, 64, 66, 67, 68, 71, 74, 77, 78, 89, 97, 100, 102, 105, 106, 107, 108, 111, 112, 118, 136, 138, 142, and 145 replaced with another amino acid;

15 (xii) the truncated analog of any of subparts (i)-(xi) having an N-terminal methionyl residue; and

(d) the OB protein or analog derivative of any of subparts (a) through (c) comprised of a chemical moiety connected to the protein moiety;

20 (e) a derivative of subpart (d) wherein said chemical moiety is a water soluble polymer moiety;

(f) a derivative of subpart (e) wherein said water soluble polymer moiety is polyethylene glycol;

25 (g) A derivative of subpart (f) wherein said water soluble polymer moiety is a polyamino acid moiety;

30 (h) a derivative of subpart (g) wherein said water soluble polymer moiety is attached at solely the N-terminus of said protein moiety;

(i) an OB protein, analog or derivative of any of subparts (a) through (h) in a pharmaceutically acceptable carrier.

35 OB proteins, analogs and related molecules are also reported in the following publications; however, no

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representation is made with regard to the activity of any composition reported:

- 5 U.S. Patent Nos. 5,521,283; 5,532,336;
5,552,522; 5,552,523; 5,552,524; 5,554,727;
5,559,208; 5,563,243; 5,563,244; 5,563,245;
5,567,678; 5,567,803; 5,569,744; 5,569,743
(all assigned to Eli Lilly and Company);
PCT WO96/23517; WO96/23515; WO96/23514;
10 WO96/24670; WO96/23513; WO96/23516;
WO96/23518; WO96/23519; WO96/23520;
WO96/23815; WO96/24670; WO96/27385 (all
assigned to Eli Lilly and Company);
PCT WO96/22308 (assigned to Zymogenetics);
PCT WO96/29405 (assigned to Ligand
15 Pharmaceuticals, Inc.);
PCT WO96/31526 (assigned to Amylin
Pharmaceuticals, Inc.);
PCT WO96/34885 (assigned to Smithkline Beecham
PLC);
20 PCT WO96/35787 (assigned to Chiron);
EP 0 725 079 (assigned to Eli Lilly and
Company);
EP 0 725 078 (assigned to Eli Lilly and
Company);
25 EP 0 736 599 (assigned to Takeda);
EP 0 741 187 (assigned to F. Hoffman LaRoche).

To the extent these references provide for
useful OB proteins or analogs or derivatives thereof, or
30 associated compositions or methods, such compositions
and/or methods may be used in conjunction with the
present OB receptor proteins, such as for co-
administration (together or separately, in a selected
dosage schedule) or by complexing compositions to the
35 present OB protein receptors. With the above provisos,
these publications are herein incorporated by reference.

Derivatives and Formulations

The present OB protein receptor and/or OB protein (herein the term "protein" is used to include "peptide" and OB protein or receptor analogs, such as those recited infra, unless otherwise indicated) may also be derivatized by the attachment of one or more chemical moieties to the protein moiety. If the present pharmaceutical compositions contain as the active ingredient a complex of OB protein receptor and OB protein, one or both of such proteins may be derivatized. The chemically modified derivatives may be further formulated for intraarterial, intraperitoneal, intramuscular, subcutaneous, intravenous, oral, nasal, pulmonary, topical or other routes of administration. Chemical modification of biologically active proteins has been found to provide additional advantages under certain circumstances, such as increasing the stability and circulation time of the therapeutic protein and decreasing immunogenicity. See U.S. Patent No. 4,179,337, Davis et al., issued December 18, 1979. For a review, see Abuchowski et al., in Enzymes as Drugs. (J.S. Holcerberg and J. Roberts, eds. pp. 367-383 (1891)). A review article describing protein modification and fusion proteins is Francis, Focus on Growth Factors 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20, OLD, UK).

Preferably, for therapeutic use of the end-product preparation, the chemical moiety for derivatization will be pharmaceutically acceptable. A polymer may be used. One skilled in the art will be able to select the desired polymer based on such considerations as whether the polymer/protein conjugate will be used therapeutically, and if so, the desired dosage, circulation time, resistance to proteolysis, and

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other considerations. For the present proteins and peptides, the effectiveness of the derivatization may be ascertained by administering the derivative, in the desired form (i.e., by osmotic pump, or by injection or infusion, or, further formulated for oral, pulmonary or nasal delivery, for example), and observing biological effects as described herein.

The chemical moieties suitable for derivatization may be selected from among various water soluble polymers. The polymer selected should be water soluble so that the protein to which it is attached so that it is miscible in an aqueous environment, such as a physiological environment. The water soluble polymer may be selected from the group consisting of, for example, polyethylene glycol, copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random or non-random copolymers (see supra regarding fusion molecules), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols, polystyrenemaleate and polyvinyl alcohol. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water.

Fusion proteins may be prepared by attaching polyaminoacids to the OB protein receptor or OB protein (or analog or complex) moiety. For example, the polyamino acid may be a carrier protein which serves to increase the circulation half life of the protein. For the present therapeutic or cosmetic purposes, such polyamino acid should be those which do not create neutralizing antigenic response, or other adverse response. Such polyamino acid may be selected from the

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group consisting of serum album (such as human serum albumin), an antibody or portion thereof (such as an antibody constant region, sometimes called "F_c") or other polyamino acids. As indicated below, the location of attachment of the polyamino acid may be at the N-terminus of the OB protein moiety, or other place, and also may be connected by a chemical "linker" moiety to the OB protein.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 2 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog).

The number of polymer molecules so attached may vary, and one skilled in the art will be able to ascertain the effect on function. One may mono-derivatize, or may provide for a di-, tri-, tetra- or some combination of derivatization, with the same or different chemical moieties (e.g., polymers, such as different weights of polyethylene glycols). The proportion of polymer molecules to protein (or peptide) molecules will vary, as will their concentrations in the reaction mixture. In general, the optimum ratio (in terms of efficiency of reaction in that there is no excess unreacted protein or polymer) will be determined by factors such as the desired degree of derivatization (e.g., mono, di-, tri-, etc.), the molecular weight of

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the polymer selected, whether the polymer is branched or unbranched, and the reaction conditions.

The chemical moieties should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art. E.g., EP 0 401 384 herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., Exp. Hematol. 20: 1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule (or other chemical moiety) may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residue. Those having a free carboxyl group may include aspartic acid residues, glutamic acid residues, and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecule(s) (or other chemical moiety). Preferred for therapeutic manufacturing purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group. Attachment at residues important for receptor binding should be avoided if receptor binding is desired.

One may specifically desire N-terminally chemically modified protein. Using polyethylene glycol as an illustration of the present compositions, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining

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the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective N-terminal chemical modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. See PCT WO 96/11953, herein incorporated by reference. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved. For example, one may selectively N-terminally pegylate the protein by performing the reaction at a pH which allows one to take advantage of the pKa differences between the ϵ -amino group of the lysine residues and that of the α -amino group of the N-terminal residue of the protein. By such selective derivatization, attachment of a polymer to a protein is controlled: the conjugation with the polymer takes place predominantly at the N-terminus of the protein and no significant modification of other reactive groups, such as the lysine side chain amino groups, occurs. Using reductive alkylation, the polymer may be of the type described above, and should have a single reactive aldehyde for coupling to the protein. Polyethylene glycol propionaldehyde, containing a single reactive aldehyde, may be used.

An N-terminally chemically modified derivative is preferred (over other forms of chemical modification) for ease in production of a therapeutic. N-terminal chemical modification ensures a homogenous product as characterization of the product is simplified relative to di-, tri- or other multi-derivatized products. The use of the above reductive alkylation process for

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preparation of an N-terminally chemically modified product is preferred for ease in commercial manufacturing.

In yet another aspect of the present invention, provided are methods of using pharmaceutical compositions of the proteins, and derivatives. Such pharmaceutical compositions may be for administration by injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, comprehended by the invention are pharmaceutical compositions comprising effective amounts of protein or derivative products of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. See, e.g., PCT WO96/29989, Collins et al., "Stable protein: phospholipid compositions and methods," published October 3, 1996, herein incorporated by reference. Hylauronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference. The compositions may be prepared in

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liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

5 Specifically contemplated are oral dosage forms of the above derivatized proteins. Protein may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least
10 one moiety to the protein (or peptide) molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the protein and increase in circulation
15 time in the body. See PCT WO95/21629, Habberfield, "Oral Delivery of Chemically Modified Proteins" (published August 17, 1995) herein incorporated by reference, and U.S. Patent No. 5,574,018, Habberfield et al., "Conjugates of Vitamin B12 and Proteins," issued
20 November 12, 1996, herein incorporated by reference.

Also contemplated herein is pulmonary delivery of the present protein, or derivative thereof. The protein (derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung
25 epithelial lining to the blood stream. See, PCT WO94/20069, Niven et al., "Pulmonary administration of granulocyte colony stimulating factor," published September 15, 1994, herein incorporated by reference.

Nasal delivery of the protein (or analog or
30 derivative) is also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those
35 with absorption enhancing agents, such as dextran or

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cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

Dosages

5 One skilled in the art will be able to ascertain effective dosages by administration and observing the desired therapeutic effect. Preferably, the formulation of the molecule or complex in a pharmaceutical composition will be such that between
10 about .10 µg/kg/day and 10 mg/kg/day will yield the desired therapeutic effect. The effective dosages may be determined using diagnostic tools over time. For example, a diagnostic for measuring the amount of OB protein or OB receptor protein in the blood (or plasma
15 or serum) may first be used to determine endogenous levels of OB protein (or receptor). Such diagnostic tool may be in the form of an antibody assay, such as an antibody sandwich assay. The amount of endogenous OB receptor protein (such as soluble receptor) is
20 quantified initially, and a baseline is determined. The therapeutic dosages are determined as the quantification of endogenous and exogenous OB receptor protein (that is, protein, analog or derivative found within the body, either self-produced or administered) is continued over
25 the course of therapy. The dosages may therefore vary over the course of therapy, with a relatively high dosage being used initially, until therapeutic benefit is seen, and lower dosages used to maintain the therapeutic benefits.

30 During an initial course of therapy of an obese person, dosages may be administered whereby weight loss and concomitant fat tissue decrease increase is achieved. Once sufficient weight loss is achieved, a dosage sufficient to prevent re-gaining weight, yet
35 sufficient to maintain desired weight or fat mass may be administered. These dosages can be determined

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empirically, as the effects of OB protein are reversible. E.g., Campfield et al., Science 269: 546-549 (1995) at 547. Thus, if a dosage resulting in weight loss is observed when weight loss is not desired, one
5 would administer a lower dose, yet maintain the desired weight.

Therapeutic Compositions and Methods

The present OB receptor proteins, alone, or in
10 combination with an OB protein, and nucleic acids may be used for methods of treatment, or for methods of manufacturing medicaments for treatment. Such treatment includes conditions characterized by excessive production of OB protein, wherein the present OB
15 receptors, particularly in soluble form, may be used to complex to and therefore inactivate such excessive OB protein. Or, such OB receptor protein, particularly in soluble form, may act to protect the activity of OB protein. While not wishing to be bound by theory, one
20 may postulate that OB protein receptor agonist activity may be accomplished by a protective effect achieved when OB protein receptor (particularly soluble receptor) is complexed to OB protein. Such effect may prolong the serum half life of OB protein in vivo. Such treatments
25 may be accomplished by preparing soluble receptor (e.g., use of an extracellular domain as described supra) and administering such composition to an individual in need thereof or by preparation of a population of cells containing or expressing such OB receptor, and
30 transplanting such cells into the individual in need thereof.

The present OB receptors may also be used for treatment of those having defective OB receptors. For example, one may treat an individual having defective OB
35 receptors by preparation of a population of cells containing such non-defective OB receptor, and

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transplanting such cells into an individual. Or, an individual may have an inadequate number of OB receptors, and cells containing such receptors may be transplanted in order to increase the number of OB
5 receptors available to an individual.

The present OB receptor proteins and related compositions such as OB receptor protein/OB protein complex, provide for weight loss, fat loss, increase in lean mass, increase in insulin sensitivity, increase in
10 overall strength, increase in red blood cells (and oxygenation in the blood), decrease in bone resorption or osteoporosis, decreased or maintained serum cholesterol level, decreased or maintained triglyceride (LDL or VLDL) levels, prevention or reduction in
15 arterial plaque formation, treatment of hypertension, and prevention or reduction of gall stone formation. As body fat composition may be correlated with certain types of cancers, the present compositions may be useful for the prevention or amelioration of certain types of
20 cancers. The present invention also includes methods for manufacture of a medicament for use in conjunction with the cosmetic/therapeutic conditions described herein, containing at least one of the present compositions.

25 The present compositions and methods may be used in conjunction with other medicaments, such as those useful for the treatment of diabetes (e.g., insulin or analogs thereof, thiazolidinediones or other antihyperglycemic agents, and possibly amylin or
30 antagonists thereof), cholesterol and blood pressure lowering medicaments (such as those which reduce blood lipid levels or other cardiovascular medicaments), and activity increasing medicaments (e.g., amphetamines). Appetite suppressants may also be used (such as
35 serotonin modulators and neuropeptide Y antagonists).

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Such administration may be simultaneous or may be in seriatim.

In addition, the present methods may be used in conjunction with surgical procedures, such as
5 cosmetic surgeries designed to alter the overall appearance of a body (e.g., liposuction or laser surgeries designed to reduce body mass, or implant surgeries designed to increase the appearance of body mass). The health benefits of cardiac surgeries, such
10 as bypass surgeries or other surgeries designed to relieve a deleterious condition caused by blockage of blood vessels by fatty deposits, such as arterial plaque, may be increased with concomitant use of the present compositions and methods. Methods to eliminate
15 gall stones, such as ultrasonic or laser methods, may also be used either prior to, during or after a course of the present therapeutic methods. Furthermore, the present methods may be used as an adjunct to surgeries or therapies for broken bones, damaged muscle, or other
20 therapies which would be improved by an increase in lean tissue mass.

In yet another aspect, the present invention provides for methods of manufacture of a medicament for the treatment of obesity, type II diabetes, excess blood
25 lipid, or cholesterol levels, increasing sensitivity to insulin, increasing lean mass, and other conditions as set forth above. Also provided are solely cosmetic treatments for individuals wishing to improve appearance by weight loss, and more specifically, loss of fat
30 deposits, even in the absence of any therapeutic benefit.

Diagnostic Compositions and Methods

As indicated supra, polypeptide products of
35 the invention may be "labeled" by association with a detectable marker substance (e.g., radiolabeled with

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125I, fluorescent, chemiluminescent, enzyme) to provide reagents useful in detection and quantification of OB receptor (or complexes) in solid tissue and fluid samples such as blood or urine. Nucleic acid products of the invention may also be labeled with detectable markers (such as radiolabels and non-isotopic labels such as biotin) and employed in hybridization processes to locate the human OB receptor gene position and/or the position of any related gene family in a chromosomal map. Nucleic acid sequences which selectively bind the human OB receptor gene are useful for this purpose. They may also be used for identifying human OB receptor gene disorders at the DNA level and used as gene markers for identifying neighboring genes and their disorders. Such nucleic acid sequences may be used for detection or measurement of OB receptor mRNA level from a biological sample. Contemplated herein are kits containing such labelled materials.

The protein and/or nucleic acids provided herein may also be embodied as part of a kit or article of manufacture. Contemplated is an article of manufacture comprising a packaging material and one or more preparations of the presently provided compositions. Such packaging material will comprise a label indicating that the protein or nucleic acid preparation is useful for detecting and/or quantifying the amount of OB receptor in a biological sample, or OB receptor defects in a biological sample. As such, the kit may optionally include materials to carry out such testing, such as reagents useful for performing DNA or RNA hybridization analysis, or PCR analysis on blood, urine, or tissue samples.

A further embodiment of the invention is selective binding molecules, such as monoclonal antibodies selectively binding OB receptor. The

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hybridoma technique described originally by Kohler and Milstein Eur. J. Immunol. 6, 511-519 (1976) has been widely applied to produce hybrid cell lines that secrete high levels of monoclonal antibodies against many specific antigens. Recombinant antibodies, (see Huse et al., Science 246: 1275 (1989)) may also be prepared. Such recombinant antibodies may be further modified, such as by modification of complementarity determining regions to increase or alter affinity, or "humanizing" such antibodies. Such antibodies may be incorporated into a kit for diagnostic purposes, for example. A diagnostic kit may be employed to determine the location and/or amount of OB receptor of an individual. Diagnostic kits may also be used to determine if an individual has receptors which bind OB protein, or those which, to varying degrees, have reduced binding capacity or ability. As stated infra, such antibodies may be prepared using immunogenic portions of an OB receptor protein. Such selective binding molecules may themselves be alternatives to OB protein, and may be formulated for pharmaceutical composition.

Such proteins and/or nucleic acids may be used for tissue distribution assays (for example, as provided in the working example below) or for other assays to determine the location of OB receptor.

The present OB receptor protein family may be used in methods to obtain OB protein analogs, mimetics or small molecules. One would simply prepare a desired OB receptor protein, particularly one with capability of binding to native OB protein, and assay the test molecule, which may be labelled with a detectable label substance, for ability to bind to such receptor. Other parameters, such as affinity, and location of binding, may also be ascertained by methods available to those skilled in the art. For example, one could use portions of the present OB receptors, particularly portions in

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the extracellular domain which are necessary for ligand binding, to determine the location of such binding. One could prepare OB receptors which have various truncations or deletions of regions of the extracellular domain which could be used to determine the location of test molecule binding. One could use an OB receptor known to be defective in native OB binding, such as potentially one from an individual having such defective receptors, and use this as the basis for ascertaining OB protein which would be effective to result in desired biological activity (i.e., weight loss, reduction in blood dyslipidemias or lowering of cholesterol levels, reduction in incidence or severity of diabetes). Other uses include solely cosmetic uses for alteration of body appearance, particularly the removal of fat.

The present OB receptor protein or nucleic acids may also be useful to identify substances which "up-regulate" OB protein or receptor. For instance, the temporal expression of OB receptor *in vivo* may be useful to determine if an administered substance causes an increase or decrease in OB receptor. One may conclude that an increase in OB receptor expression results in modulation of weight or lipid metabolism.

The divergence in the C-terminus may represent OB receptors with different signal transduction abilities. Therefore the different receptor family members may be used for different assays, depending on the type of signal transduction observed. It is thought that at least a portion of the intracellular domain is necessary for signal transduction (see supra).

The following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof.

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EXAMPLE 1: IDENTIFICATION OF HUMAN OB RECEPTOR PROTEIN

Human OB receptor protein DNA was identified
5 in a human liver cDNA library in two steps. The first
step used two primers in polymerase chain reaction (PCR)
to amplify a selected 300 base pair region from the
human liver cDNA library. The second step used the PCR
10 fragment as a probe to screen the human liver cDNA
library. Thirteen clones were obtained, but these were
incomplete at the 5' end. A procedure was performed to
complete the 5' end to make complete clones. Twelve
clones were sequenced. These twelve clones were
15 identified as either "A", "B" or "C" as denoted by the
C-terminus of the predicted amino acid sequence.

Polymerase Chain Reaction.

The original PCR primer was based on the 5'
end and the 3' end of a 416 base pair sequence having
20 GenBank Database Accession No. T73849. This sequence
was selected on the basis of a known motif present in
cytokine receptors, "WSXWS".

The 5' primer had the sequence 73-96 of the
416 bp sequence. The 3' primer had the sequence 337-360
25 of the 416 bp sequence.

These primers were used to probe a human cDNA
liver library (Stratagene). Standard methods were used.

This resulted in a PCR fragment having the
sequence 73-360 of the 416 bp fragment.
30

Hybridization.

The 300 bp PCR fragment was used to probe a
human liver cDNA library (Stratagene) using standard
methods. This second hybridization resulted in 13
35 positive clones. These were partial clones, incomplete
at the 5' end.

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Completion of the 5' end.

Rapid Amplification of cDNA End ("RACE", kit, GIBCO/BRL) was used to obtain the full length clones.

5

Sequencing results.

Sequencing revealed the three types of OB receptor DNAs. Of the thirteen clones, 4 clones were the "A" type (Seq. ID Nos. 1 and 2); 1 clone was the "B" type (Seq. ID Nos. 3 and 4) and 4 clones were of the "C" type (Seq. ID Nos. 5 and 6).

As can be seen from the Sequence Identifications (below), OB receptor A is 896 amino acids long, "B" is 904 amino acids long, and "C" is 958 amino acids long. These different OB receptors are identical at amino acid positions 1-891, and diverge almost completely beginning at position 892. The leader sequence is postulated to be, by hydrophobicity analysis, amino acids 1-21(M-A), 1-22(M-F) or 1-28(M-I), with the mature protein beginning at positions 22(F), 23(N) or 29(T). Based on hydrophobicity analysis, the leader sequence is most likely to be at positions 1-21(M through A). Chinese Hamster Ovary Cell ("CHO") cell production of the secreted form of OB receptor protein also produced a protein having amino acid number 22 as the first amino acid of the mature protein. The transmembrane region is likely to begin at either position 840 (A) or 842(L) through position 862(I), 863(S) or 864(H). For OB receptor type "A", the last amino acid is located at position 896 and is a lysine (L). For OB receptor type "B", the last amino acid is located at position 904 and is a glutamine (Q). For OB receptor type "C", the last amino acid is located at position 958 and is glutamic acid (E).

For OB receptor protein type "C", the C-terminal region possesses high homology to a known human

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transposable element. From nucleotide 2737 through 2947 of the present human OB receptor protein type "C", there is a 98.1% homology with a 211 base section of a human retrotransposable element described in Ono et al., Nucl. Acids Res. 15: 8725-8737 (1987) (bases 520 through 731, SINE-R11, GENBANK accession no. x07417).

EXAMPLE 2: TISSUE DISTRIBUTION

10 Tissue distribution was ascertained using two methods. The first method involved using the entire type "A" OB receptor. The second method involved using probes which are specific to the C-terminal region of the protein. Since these C terminal regions are divergent, the second method detected the tissue distribution of the different members of the OB receptor family.

15 The first method used a Northern Blot kit (Clontech), using the entire type A OB receptor DNA as a probe. The second method used PCR with primers specific to the nucleic acids encoding the divergent C terminus of the three types. Standard methods were used.

Table 2 shows the results for the Northern Blot and the PCR methods. The "+" indicates the investigator's subjective determination of the strength of signal. For the Northern Blot analysis, a triple "+++" indicates that a result (a dark "band" on the X-ray film) was seen upon overnight exposure of the film. A double "++" indicates that bands were seen at two weeks of exposure. A single "+" indicates that the bands were seen after three weeks of exposure. In addition, using this method, two molecular weights were observed, one at 4 Kb and one at 6.2 Kb. Although distribution was ubiquitous, the strongest signals were seen for ovary, heart and liver. For the PCR analysis, OB receptor "A" was seen in all tissue types tested (prostate, ovary, small intestine, heart, lung, liver

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and skeletal muscle), type "B" was seen only in lung and liver, and type "C" was seen in ovary, heart, lung and liver.

5

Table 2

Tissue Distribution of the Novel OB Receptor

	Northern Blot		PCR		
	4 Kb	6.2 Kb	A	B	C
Spleen	-	+			
Thymus	-	+			
Prostate	-	+	+	-	-
Testis	-	+			
Ovary	-	+++	+	-	+
Small Intestine	-	++	+	-	-
Colon	-	-			
Peripheral blood Leukocyte	-	-			
Heart	-	+++	+	-	+
Brain	-	-			
Placenta	-	+			
Lung	+	++	+	+	+
Liver	+++	+++	+	+	+
Skeletal Muscle	-	++	+	-	-
Kidney	-	++			
Pancreas	-	+			

10

EXAMPLE 3: IDENTIFICATION OF HUMAN OB RECEPTOR GENOMIC DNA AND CHROMOSOME LOCALIZATION; IDENTIFICATION OF HUMAN OB RECEPTOR "D"

15

The full length human OB receptor genomic DNA was also prepared. OB receptor "A" cDNA, in its entirety, was used as a probe against a human genomic DNA library, using materials and methods from a commercially available kit (Genome Systems, using a human genomic library in a P1 vector). A single

20

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positive clone was detected. There are introns located at (with respect to OB receptor "A" DNA) base pair number: 559, 1059, 1350, 1667, 1817, 1937, 2060, 2277, 2460, 2662, and 2738.

5 The human OB receptor gene was localized to human chromosome 1P31 by FISH analysis (Genome Systems). Human chromosome 1 is thought to correspond to mouse chromosome 4C7, which is presumed to be the location of the *db* locus.

10 A further chromosomal sequence was isolated. This chromosomal DNA sequence was isolated from a human genomic library as described above. This chromosomal sequence encodes what is here denominated human OB receptor "D", and the encoded amino acid sequence is set
15 forth in SEQ. ID No. 7. A cDNA encoding this amino acid sequence is set forth in SEQ. ID No. 8. The chromosomal DNA intron/exon junction map is set forth as SEQ. ID No. 9.

 As with forms "A", "B", and "C", for the
20 present form "D" OB receptor protein, the first amino acid of the mature protein is likely (using hydrophobicity analysis) to begin at position 22 (F), 23 (N) or 29 (T). The last amino acid of the protein is at position 1165 and is a valine residue. As with the
25 other forms, the extracellular domain extends from position 22 (F), 23 (N) or 29 (T) to position 839 (D) or 841 (G). The transmembrane domain appears to begin at position 840 (A) or 842 (L). The end of the transmembrane domain appears to be located at position
30 862 (I), 863 (S) or 864 (H). The C-terminal region, beyond the transmembrane region, is likely to be involved in signal transduction, and is located at position 863 (S), 864 (H) or 865 (Q) through position 1165 (V).

35 The present OB receptor form "D" is identical to that published by Tartaglia et al, Cell 83: 1263-1271

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(December 29, 1995) with the exception of a single amino acid change at amino acid position 976 (nucleotide codon beginning at position 3022). The present type "D" amino acid at position 976 is aspartic acid, and the published amino acid corresponding to the same position is alanine. This is a non-conservative substitution, see infra, and since the location of the substitution is within a region thought important for signal transduction, this change could affect the function of the molecule.

EXAMPLE 4: PREPARATION OF SOLUBLE OB RECEPTOR

Three forms of soluble human OB receptor have been prepared:

1. Leader + Extracellular Domain (Seq. ID Nos. 10 and 11): A recombinant form of the soluble human OB receptor was prepared. This form encompasses, in the immature protein, the leader sequence and the extracellular domain (amino acids 1-839). The mature protein would have the leader sequence deleted, and the first amino acid of the mature recombinant soluble human OB receptor would be 22 (F), 23 (N) or 29 (T). This protein was expressed as described below.

2. Leader + Extracellular Domain + C-terminal FLAG (Seq. ID No. 12): A second form of the recombinant soluble human OB receptor was also prepared. This form had a "FLAG" tag located at the "C" terminus of the protein. The "FLAG" peptide is a useful research tool as it allows one to follow the protein using an antibody which recognizes the "FLAG" peptide. Such reagents are commercially available (IBI, New Haven, CT). This protein was expressed as described below.

3. Native Splice Variant (Seq. ID Nos. 13 and 14): This form is believed to be the recombinant form of a naturally occurring secreted,

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soluble human OB receptor. This form has most of the amino acids found in the extracellular domain (amino acids 22-798), and a unique 6 amino acid sequence at the carboxyl terminus. Beginning at amino acid position 799
5 of Seq. ID No. 13, the amino acid sequence of this native splice variant human OB receptor protein is "G K F T I L."

EXAMPLE 5: PREPARATION OF EXPRESSION VECTORS

10

Recombinant human OB receptor expression vectors have been prepared for expression in mammalian cells. As indicated above, expression may also be in non-mammalian cells, such as bacterial cells. The type
15 "A" cDNA (Seq. ID No. 2) was placed into a commercially available mammalian vector (pCEP4, Invitrogen) for expression in mammalian cells, including the commercially available human embryonic kidney cell line, "293".

Recombinant human OB receptor expression
20 vectors have been prepared for expression of recombinant soluble OB receptor, consisting of the leader sequence and the extracellular domain (Seq. ID Nos. 10 and 11), using the same system as above (the commercially available mammalian vector pCEP4, and "293" cells).
25 This recombinant soluble human OB receptor was also expressed in CHO cells in a similar way.

The "FLAG-tagged" form (Seq. ID No. 12) of the recombinant soluble human OB receptor, and the "D" form (Seq. ID No. 7) were also expressed in "293" cells in a
30 similar fashion as above.

Detection of desired protein was accomplished using BIACORE (Pharmacia) analysis. This analysis is analogous to that described in Bartley et al., Nature
368: 558-560 (1994).

35

Essentially, the BIACORE machine measures affinity interactions between two proteins. In this

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case, the OB protein was immobilized on the machine, and conditioned media from cell lines expressing the OB receptor was added to the machine. Any receptor protein present in the conditioned media bound to the OB protein surface. The BIACORE machine gave a read-out indicating that receptor protein was being expressed. For recombinant soluble receptor (Seq. ID No. 10) expression in "293" cells, the read-out was 191.0 relative to a baseline readout of 0. For recombinant soluble receptor (Seq. ID No. 10) expression in CHO cells, the read-out was 150.9 relative to a baseline readout of 0. For recombinant soluble receptor with a C-terminal FLAG-tag (Seq. ID. No. 12), the read-out was 172.0 relative to a baseline of 0.

For expression in bacterial cells, one would typically eliminate that portion encoding the leader sequence (e.g., potentially amino acids 1-21, 1-22 or 1-28). One may add an additional methionyl at the N-terminus for bacterial expression. Additionally, one may substitute the native leader sequence with a different leader sequence, or other sequence for cleavage for ease of expression.

EXAMPLE 6: DEMONSTRATION OF SIGNAL TRANSDUCTION

25

This example demonstrates that the "D" form is active to produce a signal within a cell, whereas in the same cell type, the "A" form does not. The signal transduction assay was performed by the use of "293" cells transiently expressing either the "A" or the "D" form (see above for preparation of the "293" expression clones). Phosphorylation of molecules predicted to be involved in signal transduction within the cell was examined upon OB protein binding to the OB receptor protein tested. The results demonstrate that upon binding of OB protein to the extracellular domain, the

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"D" form of the present OB protein receptor transduces a signal sufficient to initiate phosphorylation of signalling molecules.

5 Methods

1. OB receptor molecules. As indicated above, the "A" form (Seq. ID No. 1) and the "D" form (Seq. ID. No. 7) were studied.

2. Expression system. The pCEP 4 system (as described above) having inserted DNA encoding the "A" form (Seq. ID No. 2) or the "D" form (Seq. ID No. 8) was used to transfect "293" cells. These cells did not allow for the pCEP4 vector to integrate into the genome, so such expression was transient. Non-recombinant (mock-transfected) cells were also prepared as controls.

3. Detection of phosphorylation. Mock transfected cells and cells expressing the "A" form or the "D" form were analyzed. Prior to treatment the cells were serum-starved by incubation in media with 0.5% serum for 16 hours prior to the treatments. The cells were treated with the OB protein (10 mg/ml) for 15 minutes at 37°C, after which the cells were lysed in modified NP40 buffer (50 mM Tris, pH 8.0, 150 mM sodium chloride, 1% NP40, 10 mg/ml aprotinin, 5mM EDTA, 200 mM sodium orthovanadate). Phosphotyrosine containing proteins were immunoprecipitated (Anti-phosphotyrosine antibody 4G10, UBI, Lake Placid, NY), and separated by SDS polyacrylamide gel electrophoresis. After electrophoresis and electroblotting to membranes the immunoprecipitates were probed with antibodies to various signal transduction molecules. Antibodies to STATs, JAKs and ERKs were purchased from Santa Cruz Biotechnology Inc. Immune complexes were detected by horseradish peroxidase conjugated secondary reagents using chemiluminescence as described by the manufacturer (ECL, Amersham). As a positive control, 32D cells were

treated with IL-3, which is known to activate by tyrosine phosphorylation most of the molecules being analyzed.

4. Results. Results are presented in Table 3, below. As can be seen, only the "D" form was able to respond to either mouse or human OB protein as detected by phosphorylation of JAK and STAT molecules. A "+" designation indicates signal was detected, a "-" designation means that no signal was observed.

10

TABLE 3

Signal /AB†	293 Alone	293/D hrOB*	293/D mrOB**	293/A hrOB#	293/A mrOB##	32D IL-3
STAT1	-	+		-	-	+
STAT3	-	+	+			+
STAT5	-	+	+		-	+
JAK1	-	+	+	-	-	+
JAK2	-	+	+			-
JAK3	-	-	-			-
TYK2	-	+	+		-	+
ERKs 1,2	-	-	-	-	-	

† Antibody detection target

- 15 * 293 cells expressing receptor form "D", treated with recombinant human OB

** 293 cells expressing receptor form "D" treated with recombinant murine OB

293 cells expressing receptor form "A" treated with recombinant human OB

- 20 ## 293 cells expressing receptor form "A" treated with recombinant murine OB

The "D" form is capable of initiating signalling through the JAK/STAT pathways in 293 cells, whereas the "A" form cannot.

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EXAMPLE 7: USE OF SOLUBLE OB RECEPTOR AS A THERAPEUTIC

5 This example demonstrates that soluble OB
receptor protein acts to protect the activity of OB
protein. Below, soluble OB receptor and/or OB protein
was delivered to a mammal via "gene transplant" -- that
is, via bone marrow cells engineered to express the
desired DNAs. When soluble OB receptor combined with OB
10 protein was delivered, the animals lost more weight than
delivery of OB protein alone. This demonstrates the
protective activity of OB receptor protein.

While not wishing to be bound by theory, one
explanation of the mode of action is that soluble OB
15 receptor protein acts to protect the OB protein in serum
from agents or conditions which could diminish its
activity. The protective action appears to increase
circulating half-life of the protein. As such, the
present example demonstrates that OB receptor either
20 alone, or administered as a complex with OB protein (or
analog or derivative thereof) could act as a therapeutic
agent.

Materials and methods:

25 1. Preparation of recombinant ob retroviral
vector Packaging Cells.

Use of murine ob cDNA. Full length wild-type
murine ob cDNA was amplified by the PCR using synthetic
oligonucleotides designed from the published sequence
30 Zhang et al., Nature 372: 425-432 (1994). Linkers (An Eco
RI linker and a Bgl II linker) were used to facilitate
subcloning.

Use of soluble recombinant human OB receptor
cDNA. Methods similar to those above were used. A
35 construct containing the recombinant human soluble
receptor of Seq. ID No. 10 was used, and modified with

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linkers to facilitate cloning (i.e., the addition of a Bgl II restriction endonuclease recognition site).

Placement of desired cDNA into vector. PCR products were digested with *Eco*RI and *Bgl*II and cloned into similarly-digested parental vector (pMSCV2.1) under the transcriptional control of the viral LTR promoter. The parental MSCV vector (supplied by R. Hawley, University of Toronto, Canada) was derived from MESV (murine embryonic stem cell virus) and contains a neomycin phosphotransferase resistance (*neo*^r) gene driven by an internal mouse phosphoglycerate kinase (PGK) promoter, as described: Hawley, et al, J. Exp. Med. 176: 1149 -1163 (1992). The parental plasmid pMSCV2.1 and pMSCV-OB were independently electroporated into the GP+E-86 packaging cell line (supplied by Dr. A. Bank, Columbia University, NY) Markowitz et al., J. Virol. 62:1120-1124 (1988). Transient supernatants were harvested from electroporated populations and used to infect tunicamycin treated parental GP+E-86 cells. Tunicamycin treatment relieves the block to superinfection of the parental packaging cells. G418 (0.78 mg/mL, 67% active, GIBCO Laboratories, Life Technologies, Inc., Grand Island, NY) resistant clones were selected from each infected population and titered by infection of NIH3T3 cells. Clones with the highest G418 resistant titer were expanded and frozen as aliquots. Each bone marrow infection and transplantation experiment used aliquots from the same passage of frozen viral packaging cells. Both the parental and ob packaging cell lines were tested for the presence of, and found to be free from, replication competent virus using a sensitive marker rescue assay. Moore, et al., (1993) in: Gene Targeting: A Practical Approach, Joyner, Ed. (Oxford University Press, New York, NY).

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2. Production of Retroviral Supernatants.

Recombinant virus-producing packaging cell lines were grown in 175cm² tissue culture flasks in Iscove's Modified Dulbecco's Medium (IMDM) (GIBCO), 10% (v/v) FBS, at 37°C. Sub-confluent (approximately 60%) monolayers of cells were fed with fresh medium 24h prior to harvest of virus-containing supernatants. Viral supernatants were removed from packaging cell lines by aspiration, sterile filtered (0.45µm) and added directly to bone marrow cultures. Fresh aliquots of frozen packaging cell lines were thawed for use in each experiment.

3. Bone Marrow Infection and Transplantation.

Eight to 12-week old female C57BL/6J (+/+) or (ob/ob) mice were used as bone marrow donors and recipients. All mice were purchased from The Jackson Laboratory (Bar Harbor, ME) and housed under specific pathogen-free conditions in a vivarium in accordance with governmental regulations and institutional guidelines.

Bone marrow cells were harvested from femurs and tibias of donor mice 4 days post 5-fluorouracil (5-FU, Sigma Chemical Co., St. Louis, MO) treatment (150 mg/kg i.v.). Bone marrow cells (6×10^5 /mL) were incubated in 150mm tissue culture dishes (30mL/dish) containing fresh viral supernatant (as described above), 15% FBS, 6 mg/mL polybrene (Sigma), 0.1% bovine serum albumin (BSA, Fraction V, Sigma), 2.5 ng/mL recombinant mouse IL-3 (rmIL-3), 100 ng/mL each of recombinant human IL-6 (rhIL-6), recombinant human IL-11 (rhIL-11), and recombinant rat SCF (rrSCF). All growth factors were produced by Amgen, Inc. (Thousand Oaks, CA). Culture media were replaced daily for 3 days with fresh virus-containing supernatant and growth factors.

At the end of the infection period, total non-adherent and adherent cells were washed and resuspended in 1% BSA-saline and transplanted into g-irradiated (12

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Gy, Cs¹³⁷) mice. Each animal was transplanted with 2.5×10^6 syngeneic cells. There were approximately 10 animals per cohort.

4. Analysis of OB protein expression in
5 transfected cells and transplanted animals. For
transfected bone marrow cells, Western analysis was
performed. Vector packaging cell supernatant was
resolved by SDS-PAGE (16% acrylamide), then transferred
to Hybond-ECL (Amersham, Arlington Heights, IL). The
10 filter was incubated with affinity-purified rabbit a-
mouse OB protein polyclonal antibody (1mg/mL) in T-TBS
buffer (20mM Tris-chloride, pH7.6, 137mM NaCl, 0.1%
Tween20) at room temperature for 45 min. Horseradish
peroxidase (HRP)-conjugated donkey a-rabbit IgG
15 (Amersham) was diluted in T-TBS (1:2500) and incubated
with the filter at room temperature for 45 min.
Enhanced chemiluminescence (ECL, Amersham) detection was
performed as recommended by the manufacturer.

For transplanted animals, serum was analyzed.
20 Animals were bled retroorbitally, under isofluorane
anesthesia. Serum from transplanted ob/ob animals was
resolved by SDS-PAGE (4-20% acrylamide) under non-
reducing and reducing conditions, then transferred to
Trans-Blot (Bio-Rad Laboratories, Hercules, CA)
25 membranes. The membranes were incubated for 2 hours at
room temperature with HRP-conjugated rabbit a-mouse OB
protein antibody (0.125mg/mL) in T-TBS buffer containing
5% fetal bovine serum and 1% bovine serum albumin.
Bound OB protein was detected by ECL (Amersham),
30 performed as recommended by the manufacturer.

For quantitation of soluble OB protein levels,
serum from transplanted animals was subjected to ELISA
analysis. Briefly, affinity-purified rabbit a-OB
protein polyclonal antibody was coated onto 96-well
35 plates. Standards (purified recombinant OB protein

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monomer, Pelleymounter et al., Science 269: 540-543 (1995) and experimental samples were added, and the plates were incubated at room temperature. The plates were washed twice and affinity-purified rabbit a-OB protein antibody conjugated to horseradish peroxidase was added. Following incubation at room temperature, the plates were washed four times with TNE-Tween20. TMB/peroxide substrate was added and the color reaction was read at 450nm in a Molecular Devices plate reader. OB protein concentrations in sera were estimated by comparison to a standard curve prepared from internal standards. OB protein levels were reliably measured in samples containing >160 pg/mL.

5. Body Weight and Food Intake. Mice were offered pelletized rodent chow (PMI Feeds, Inc., St. Louis, MO) ad libitum. The body weight of individual animals was measured daily for the first two months of analysis, and weekly thereafter. Food consumption was measured daily on selected groups of individually-housed animals.

Results

Results are presented in Tables 4 and 5 below. Administration of OB protein receptor increased the effectiveness of OB protein. This may have been accomplished via an increased circulation time of OB protein in the presence of OB protein receptor.

As can be seen in the Table, animals administered a combination of OB protein and OB protein receptor (via genetic therapy) had a greater weight loss after 28 days than either composition alone. The Table presents the results of two experiments ("___/___"). As can be seen, use of the OB protein alone at day 40 resulted in animals with 87.5% and 72.2% of the starting weight. Using OB receptor in combination with OB protein, however, resulted in animals with 68% and

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53.6% of the starting weight. Use of the receptor alone appeared to have little effect, if any.

TABLE 4

5

Treatment	Weight (g) decrease at day 28 (ave)	% starting weight (ave) day 28	% starting weight (ave) day 40
OB alone*	6.3/12.7	87.9/75.3	87.5/72.2
Receptor** alone	[1.4]/[0.3]	103/100.6	104.2/101.7
OB + Receptor***	12.6/16.8	76.3/67.5	68/53.6

* 50% bone marrow cells transfected with OB protein cDNA as described above, and 50% bone marrow cells without genetic alteration

10 ** 50% bone marrow cells transfected with OB receptor protein cDNA as described above, and 50% bone marrow cells without genetic alteration

15 *** 50% bone marrow cells transfected with OB protein cDNA as described above, and 50% bone marrow cells transfected with OB receptor protein cDNA as described above.

20 Table 5, below, contains results of the OB levels found in the serum from animals administered OB protein alone, or administered OB protein in combination with OB protein receptor (via the "gene therapy" method of this example). The data reflect nanograms of OB protein per milliliter of serum, plus or minus the standard error of the mean.

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TABLE 5

Treatment	Experiment #1†	Experiment #2‡
OB alone*	2.93 +/- 0.77	9.74 +/- 1.02
Receptor** alone	0.08 +/- 0.05	0.12 +/- 0.07
OB + Receptor***	12.11 +/- 1.90	15.18 +/- 2.52

* 50% bone marrow cells transfected with OB protein
5 cDNA as described above, and 50% bone marrow cells
without genetic alteration

** 50% bone marrow cells transfected with OB receptor
protein cDNA as described above, and 50% bone marrow
cells without genetic alteration

10 *** 50% bone marrow cells transfected with OB protein
cDNA as described above, and 50% bone marrow cells
transfected with OB receptor protein cDNA as described
above.

† Experiment #1 was conducted as described above,
15 with OB protein serum levels measured after 38 days.

‡ Experiment #2 was also conducted as described
above, with OB protein serum levels measured after 24
days.

The data demonstrate the protective effects of
20 OB receptor. As can be seen, in the presence of OB
receptor, OB protein has a higher accumulation in the
serum. The degree of accumulation is observed to
increase inversely with the levels of OB protein in the
serum. In Experiment #1 (with a base OB protein level
25 of about 2.93 ng/ml), the OB protein serum level
increased about 400% with the addition of receptor,
where in Experiment #2 (with a base of about 9.74), the
OB protein serum level increased by about 25%.

OB receptor administered either alone or in
30 association with OB protein (or analogs or derivatives

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thereof) may serve to increase the circulation time of OB protein, and therefore enhance the therapeutic efficacy of either exogenous or endogenous OB protein.

5 EXAMPLE 8: PREPARATION OF SELECTIVE BINDING MOLECULES

Animals were immunized for the preparation of polyclonal antibodies using the following peptides (with respect to the numbering of the amino acids for OB receptor A, Seq. ID No. 1): 54-64; 91-100; 310-325;
10 397-406; 482-496; 874-885; and, with respect to amino acids of OB receptor "C" (Seq. ID No. 5), 910-929. Some of the polyclonal antibodies prepared (in rabbits) were tested for ability to bind to recombinant human OB receptor protein. The polyclonal antibody prepared
15 against amino acids 54-64 was found to have the highest affinity for recombinant human OB receptor protein. The polyclonal antibody prepared against amino acids 397-406 was also found to bind to recombinant human OB receptor protein. The polyclonal antibody prepared against amino
20 acids 91-100 was found to slightly bind to recombinant human OB receptor protein. The polyclonal antibody prepared against amino acids 874-885 was found not to bind to recombinant human OB receptor protein.

An additional study was performed which
25 demonstrates the expression and purification of the extracellular domain of the OB receptor protein in CHO cells, and antibodies which recognize this OB protein receptor extracellular domain.

The extracellular domain of the human OB
30 receptor protein was expressed as a secreted, soluble protein in CHO cells as previously described supra. Individual cell lines were isolated and grown in increasing amounts of methotrexate to increase selection/expression of the recombinant receptor protein
35 (100, 200 or 500 micrograms methotrexate per ml of media). Conditioned media from the CHO cell lines was

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collected, and the proteins in the conditioned media were fractionated by SDS-PAGE. The OB receptor extracellular domain migrated as a broad band with an apparent size range of about 140 kDa to about 200 kDa.

5 The OB receptor protein extracellular domain was detected by Western Blot analysis using polyclonal antibodies prepared against a portion of the extracellular domain of the OB receptor protein. The unfolded, bacterially expressed protein was used as an antigen to
10 generate antisera in rabbits. The identified OB receptor extracellular domain was purified by affinity chromatography. The purified protein was sequenced at the amino terminus to confirm that it was the OB
15 protein (after signal peptide cleavage) as expressed in CHO cells. It was found that amino acid no. 22 (according to the amino acid sequence numbering of Seq. ID No. 1, *infra*), was the first amino acid of the mature protein as expressed in CHO cells.

20 Other immunogenic peptides may be used. Polyclonal, monospecific polyclonal, monoclonal, antibody fragments, and recombinant antibodies may be prepared using methods available to those skilled in the art.

25 One may further use recombinant techniques or peptide synthesis methods to alter the character of such selective binding molecules. This may be accomplished by preparing recombinant antibodies having altered complementarity determining regions (sometimes referred
30 to in the art as "CDR's") to, for example "humanize" the antibodies by using human Fc (constant) regions. Other types of recombinant antibodies, for example, those having CDR's altered to enhance affinity or selectivity to one or more members of the OB receptor family, may be
35 prepared and used using methods available to those

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skilled in the art. See Winter et al., Nature 349: 293-299 (1991).

The present OB receptor protein may be used as an assay to screen for desired selective binding molecules. Such assay may be based on binding capability, or biological activity, or, other means of detecting signal transduction. For example, if one were to prepare a series of modified antibodies, one could test them for affinity (i.e, binding strength) against the target OB receptor.

The selective binding molecules may be useful for diagnostic purposes, such as tissue distribution analysis, or to diagnose the relative affinity of an individual's OB receptors for such selective binding molecule to determine the functionality of an individual's OB receptor during a course of therapy. Selective binding molecules may be alternative therapeutic or cosmetic products to OB protein.

20 EXAMPLE 9: GENE THERAPY

One may deliver the present OB receptor protein via gene therapy, as described infra.

One may envision, using materials and methods available to those skilled in the art and provided herein, using T-cells as an agent carrying DNA expressing OB receptor for gene therapy. An individual would have T-cells selected using CD34+ selection and a magnetic microparticles selection device. Such cells would be transfected with the desired DNA, or the regulation of the desired coding region may be altered using homologous recombination or other in situ techniques. The transduced cells could be selected empirically, using means to detect the desired protein, or a marker may be included which permits indirect detection (i.e., a selectable marker as is known in the

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art). Optionally, such cells could be expanded, for example, using one or more growth factors such as SCF or an interleukin, and such cells could be stored for future use. In such a way, the procedure would only
5 have to be accomplished once or infrequently in an individual's lifetime, for later transfer into the individual. The cells would be re-planted into the individual, and the individual would be monitored for desired therapeutic effect, such as weight
10 loss/maintenance of weight, diabetes recurrence, blood lipid levels, or other conditions.

Illustrative Nucleic Acid and Amino Acid Sequences

The below amino acid and DNA sequences are
15 those to which reference has been made. An asterick("*") indicates the position of a stop codon.

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Human OB Receptor "A" Amino Acid Sequence (Seq. ID No. 1 (Amino Acid, single letter abbreviation)):

1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP
5 51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS
101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN
10 151 LFRNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD
251 GNLKISWSSP PLVPFPLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP
15 301 GSSYEVQVRG KRLDGPPIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSF
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK
20 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSII PISEPKDCYL QSDGFYECIF
501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN
25 551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK
701 FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN
751 SSCVIVSWIL SPSDYKL MYF IIEWKNLNED GEIKWLRISS SVKKYYIHDH
35 801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII
851 SSSILLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KRTDIL*SLI
40 901 MITTDEPNVP TSQQSIEY*K IFTF*RRGAN LKKIQLNF*E LTYGGLC*FR
951 T*NRCVNLGS KCRFESSLDV *L

Human OB Receptor "A" DNA Sequence (Seq. ID No. 2 (DNA)):

1 CCGCCGCCAT CTCTGCCTTC GGTCGAGTTG GACCCCCGGA TCAAGGTGTA
5 51 CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA
101 TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTC A TATCCAATTA
151 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC
10 201 TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA ATTCGAATGG
251 ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT
15 301 TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA
351 GATAGAAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT
401 TTCAACAGTA AATTCTTTAG TTTTTCACA AATAGATGCA AACTGGAACA
20 451 TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG
501 TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT
25 551 ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAG
601 GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTCATGA ATGTTGTGAA
651 TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC TCCTTATGTG
30 701 TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG
751 TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG
35 801 GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT
851 GGTACCATTT CCACTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA
901 CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA
40 951 GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG
1001 ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA
45 1051 CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG
1101 TCTAATGTTT CTTTTCCTG CATCTATAAG AAGGAAAACA AGATTGTTCC
1151 CTCAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAAA
50 1201 GCCAGTATGA TGTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT
1251 CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGACTG

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1301 CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG
1351 ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG
5 1401 ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT
1451 GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA
10 1501 TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT
1551 TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG
1601 GATTAGGATC AATCACTCTC TAGGTTCACT TGA CTCTCCA CCAACATGTG
15 1651 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA
1701 GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT
20 1751 CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGAA
1801 AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT
1851 GTCAGTCTCC CAGTTCAGAG CTTGTGTGCA GTCTATGCTG TTCAGGTGCG
25 1901 CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG
1951 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT
30 2001 TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT
2051 ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT
2101 ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG
35 2151 GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG CACATACTGT
2201 TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT
40 2251 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCAC TCAGT
2301 GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC
2351 CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGA AAA AATCTTAATG
45 2401 AAGATGGTGA AATAAAATGG CTTAGAATCT CTTCACTGT TAAGAAGTAT
2451 TATATCCATG ATCATTTTAT CCCCATGAG AAGTACCAGT TCAGTCTTTA
50 2501 CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA
2551 CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT

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2601 GTGCCAGTAA TTATTTCTC TTCCATCTTA TTGCTTGGAA CATTATTAAT
2651 ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA
5 2701 AGAATTGTTC CTGGGCACAA GGACTTAATT TTCAGAAGAG AACGGACATT
2751 CTTTGAAGTC TAATCATGAT CACTACAGAT GAACCCAATG TGCCAACTTC
2801 CCAACAGTCT ATAGAGTATT AGAAGATTTT TACATTTTGA AGAAGGGGAG
10 2851 CAAATCTAAA AAAAATTCAG TTGAACTTCT GAGAGTTAAC ATATGGTGGA
2901 TTATGTTGAT TTAGAACTTA AAATAGATGT GTAAATTTGG GTTCAAAATG
15 2951 TAGATTTGAG TCCAGTTTGG ATGTGTGATT AATTTTCAAA TCATCTAAAG
3001 TTTAAAAGTA GTATTCATGA TTTCTGGCTT TTGATTTGCC ATATTCCTGG
3051 TCATAAAACA TTAAGAAAAT TATGGCTGTT GCTGTCATTA CATATCTATT
20 3101 AAATGTCATC AAATATGTAG TAGACAATTT TGTAATTAGG TGAACCTCTAA
3151 AACTGCAACA TCTGACAAAT TGCTTTAAAA ATACAATGAT TAT

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Human OB Receptor "B" Amino Acid Sequence (Seq. ID No. 3 (Amino Acid)):

5 1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP
51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS
10 101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN
15 151 LERNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV
20 201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD
25 251 GNLKISWSSP PLVPFPLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP
30 301 GSSYEVQVRG KRLDGPPIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSE
35 351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK
40 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTGMTCRWS
45 451 TSTIQSLAES TLQLRYHRSS LYCSDIPSII PISEPKDCYL QSDGFYECIF
50 501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN
55 551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV
60 601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN
65 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK
70 701 FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN
75 751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNED GEIKWLRISV SVKKYYIHDH
80 801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII
85 851 SSSILLLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KKRLSIFLSS
90 901 IQHQ*HVVLF FWSLKQFQKI SVLIHHGKIK MR*CQQLWSL YFQQQILKRV
95 951 LFVLVTSSTV LLSLRLRVLR *PMRTKARDN PLLNTPR*SA TLNQVKLVK
45

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Human OB Receptor "B" DNA Sequence (Seq. ID No. 4 (DNA)):

1 CCGCCGCCAT CTCTGCCTTC GGTGAGTTG GACCCCCGGA TCAAGGTGTA
5 51 CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA
101 TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA
15 151 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC
201 TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA ATTCGAATGG
251 ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT
15 301 TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA
351 GATAGAAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT
20 401 TTCAACAGTA AATTCTTTAG TTTTTCACAA AATAGATGCA AACTGGAACA
451 TACAGTGCTG GCTAAAAGGA GACTTAAAAT TATTCATCTG TTATGTGGAG
501 TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT
25 551 ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAG
601 GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTCATGA ATGTTGTGAA
30 651 TGTCTTGTGC CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG
701 TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG
751 TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG
35 801 GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT
851 GGTACCATTT CCACTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA
40 901 CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA
951 GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG
1001 ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA
45 1051 CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTGGG
1101 TCTAATGTTT CTTTTCCTG CATCTATAAG AAGGAAAACA AGATTGTTCC
50 1151 CTCAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAA
1201 GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT
1251 CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGACTG

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1301 CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG
1351 ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG
5 1401 ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT
1451 GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA
10 1501 TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT
1551 TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG
1601 GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG
15 1651 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA
1701 GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT
20 1751 CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGA
1801 AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT
1851 GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG TTCAGGTGCG
25 1901 CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG
1951 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT
30 2001 TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT
2051 ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT
2101 ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG
35 2151 GGAAATCACA CGAAATTAC TTTCTGTGG ACAGAGCAAG CACATACTGT
2201 TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT
40 2251 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT
2301 GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC
2351 CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGA
45 2401 AAGATGGTGA AATAAAATGG CTTAGAATCT CTTATCTGT TAAGAAGTAT
2451 TATATCCATG ATCATTTTAT CCCCATTGAG AAGTACCAGT TCAGTCTTTA
50 2501 CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA
2551 CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT

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2601 GTGCCAGTAA TTATTTCTC TTCCATCTTA TTGCTTGGAA CATTATTAAT
2651 ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA
5 2701 AGAATTGTTC CTGGGCACAA GGACTTAATT TTCAGAAGAA ACGTTTGAGC
2751 ATCTTTTTAT CAAGCATACA GCATCAGTGA CATGTGGTCC TCTTCTTTTG
2801 GAGCCTGAAA CAATTTTCTAGA AGATATCAGT GTTGATACAT CATGGAAAAA
10 2851 TAAAGATGAG ATGATGCCAA CAACTGTGGT CTCTCTACTT TCAACAACAG
2901 ATCTTGAAAA GGGTTCTGTT TGTTTTAGTG ACCAGTTCAA CAGTGTTAAC
15 2951 TTCTCTGAGG CTGAGGGTAC TGAGGTAACC TATGAGGACG AAAGCCAGAG
3001 ACAACCCTTT GTTAAATACG CCACGCTGAT CAGCAACTCT AAACCAAGTG
3051 AAAGTGGTGA AGA

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Human OB Receptor "C" Amino Acid Sequence (Seq. ID No. 5 (Amino Acid)):

5 1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP
51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS
10 101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN
151 LFRNINYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD
15 251 GNLKISWSSP PLVPFPLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP
301 GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSF
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK
20 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF
25 501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN
551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK
701 FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN
35 751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNED GEIKWLRISV SVKKYYIHDH
801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII
851 SSSILLLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KMLEGSMFVK
40 901 SHHHSLSIST QGHKHCGRPQ GPLHRKTRDL CSLVYLLTLP PLLSYDPAKS
951 PSVRNTQE*S IKKKKKKLEG

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Human OB Receptor "C" DNA Sequence (Seq. ID No. 6 (DNA)):

1 CCGCCGCCAT CTCTGCCTTC GGTGAGTTG GACCCCCGGA TCAAGGTGTA
5 51 CTTCTCTGAA GTAAGATGAT TTGTCAAAA TTCTGTGTGG TTTTGTTACA
101 TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA
10 151 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC
201 TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA ATTCGAATGG
251 ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT
15 301 TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA
351 GATAGAAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT
20 401 TTCAACAGTA AATTCTTTAG TTTTTCACAA AATAGATGCA AACTGGAACA
451 TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG
501 TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT
25 551 ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAG
601 GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTATGA ATGTTGTGAA
30 651 TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC TCCTTATGTG
701 TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG
751 TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG
35 801 GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT
851 GGTACCATTT CCACTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA
40 901 CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA
951 GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG
1001 ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA
45 1051 CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG
1101 TCTAATGTTT CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC
50 1151 CTCAAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAAA
1201 GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT

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1251 CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGTACTG
1301 CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG
5 1351 ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG
1401 ACTTGACAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT
1451 GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA
10 1501 TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT
1551 TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG
15 1601 GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG
1651 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA
1701 GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT
20 1751 CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGAA
1801 AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT
25 1851 GTCAGTCTCC CAGTTCAGAG CTTGTGTGCA GTCTATGCTG TTCAGGTGCG
1901 CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG
1951 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT
30 2001 TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT
2051 ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT
35 2101 ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG
2151 GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG CACATACTGT
2201 TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT
40 2251 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT
2301 GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC
45 2351 CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAA AATCTTAATG
2401 AAGATGGTGA AATAAAATGG CTTAGAATCT CTTCATCTGT TAAGAAGTAT
2451 TATATCCATG ATCATTTTAT CCCCATTGAG AAGTACCAGT TCAGTCTTTA
50 2501 CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA
2551 CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT

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2601 GTGCCAGTAA TTATTCCTC TTCCATCTTA TTGCTTGGA CATTATTAAT
2651 ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA
5 2701 AGAATTGTTC CTGGGCACAA GGAATTAATT TTCAGAAGAT GCTTGAAGGC
2751 AGCATGTTCG TTAAGAGTCA TCACCACTCC CTAATCTCAA GTACCCAGGG
10 2801 ACACAAACAC TGCGGAAGGC CACAGGGTCC TCTGCATAGG AAAACCAGAG
2851 ACCTTTGTTC ACTTGTTTAT CTGCTGACCC TCCCTCCACT ATTGTCCTAT
2901 GACCCTGCCA AATCCCCCTC TGTGAGAAAC ACCCAAGAAT GATCAATAAA
15 2951 AAAAAAAAAA AAAAAACTCG AGGGGG

Human OB Receptor "D" Amino Acid Sequence (Sequence ID No. 7)

1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP
5 51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS
101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDCLKF ICYVESLFKN
10 151 LFRNINYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD
15 251 GNLKISWSSP PLVPFPLOQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP
301 GSSYEVQVRG KRLDGPPIWS DWSTPRVETT QDVIYFPPKI LTSVGSNVSF
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFNINLNETK
20 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF
25 501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVVKPLPP SSVKAEITIN
551 IGLLKISWEK PVFPENNLOF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK
701 FTFWLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN
35 751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNEG GEIKWLRISV SVKKYYIHDH
801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII
851 SSSILLGLTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KPETFELHFI
40 901 KHTASVTCGP LLEPETISE DISVDTSWKN KDEMPTTVV SLLSTTDLEK
951 GSVCSISDQFN SVNFSEAEGT EVTYEDESQR QPFVKYATLI SNSKPSETGE
45 1001 EQGLINSSVT KCFSSKNSPL KDSFSNSSWE IEAQAFFILS DQHPNIIISP
1051 LTFSEGLDEL LKLEGNFPPEE NNDKKSIIYL GVTSIKKRES GVLLTDKSRV
1101 SCFPFAPCLF TDIRVLQDSC SHFVENNINL GTSSKKTFFAS YMPQFQTCST
50 1151 QTHKIMENKM CDLTV*FH*R NLQICVIMGN IKCNRL*LWV GERKETRVKE
1201 ENNCSK*KKK KKNSRPARPD

Human OB Receptor "D" Nucleic Acid Sequence (Sequence ID No.8)

1 GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC
5 51 GGTGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT
101 TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA
151 TAACTGCGTT TAACTTGTCA TATCCAATTA CTCCTTGGAG ATTTAAGTTG
10 201 TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG
251 GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG
15 301 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA
351 ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG
401 TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCTTTAG
20 451 TTTTTCACAA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA
501 GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT
25 551 CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT
601 TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTTCA GATGGTTTAC
651 TGCAATTGCA GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC
30 701 AGCCAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG
751 GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG
35 801 AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA
851 TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTCAAT
901 ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC
40 951 AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC
1001 TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT
45 1051 GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC
1101 TTTCCACCTA AAATTCTGAC AAGTGTTGGG TCTAATGTTT CTTTTCACTG
1151 CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAAGAG ATTGTTTGGT
50 1201 GGATGAATTT AGCTGAGAAA ATTCTCAAA GCCAGTATGA TGTTGTGAGT
1251 GATCATGTTA GCAAAGTTAC TTTTTCAT CTGAATGAAA CCAAACCTCG

1301 AGGAAAGTTT ACCTATGATG CAGTGTACTG CTGCAATGAA CATGAATGCC
1351 ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA
5 1401 TGTGAAACTG ATGGGTACTT AACTAAATG ACTTGCAGAT GGTCAACCAG
1451 TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA
10 1501 GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC
1551 AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC
1601 AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC
15 1651 TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG
1701 AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG
20 1751 ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC
1801 AATTCCAGAT TCGCTATGGT TTAAGTGGA AAGAAGTACA ATGGAAGATG
1851 TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA
25 1901 CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC
1951 TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT
30 2001 ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA
2051 TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA
2101 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT
35 2151 TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC
2201 TTTCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT
40 2251 CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG
2301 AGCAAAGTAA ATATCGTGCA GTCACCTAGT GCTTATCCTT TAAACAGCAG
2351 TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT
45 2401 ATTTTATTAT TGAGTGGA AATCTTAATG AAGATGGTGA AATAAAATGG
2451 CTTAGAATCT CTTATCTGT TAAGAAGTAT TATATCCATG ATCATTTTAT
50 2501 CCCCATGAG AAGTACCAGT TCAGTCTTTA CCCAATATTT ATGGAAGGAG
2551 TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA

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2601 CACCAGAGTG ATGCAGGTTT ATATGTAATT GTGCCAGTAA TTATTTCTC
2651 TTCCATCTTA TTGCTTGGAA CATTATTAAT ATCACACCAA AGAATGAAAA
5 2701 AGCTATTTTG GGAAGATGTT CCGAACCCCA AGAATTGTTC CTGGGCACAA
2751 GGACTTAATT TTCAGAAGCC AGAAACGTTT GAGCATCTTT TTATCAAGCA
2801 TACAGCATCA GTGACATGTG GTCCTCTTCT TTTGGAGCCT GAAACAATTT
10 2851 CAGAAGATAT CAGTGTTGAT ACATCATGGA AAAATAAAGA TGAGATGATG
2901 CCAACAACCTG TGGTCTCTCT ACTTTCAACA ACAGATCTTG AAAAGGGTTC
15 2951 TGTGTGATT AGTGACCAGT TCAACAGTGT TAACTTCTCT GAGGCTGAGG
3001 GTACTGAGGT AACCTATGAG GACGAAAGCC AGAGACAACC CTTTGTTAAA
3051 TACGCCACGC TGATCAGCAA CTCTAAACCA AGTGAACTG GTGAAGAACA
20 3101 AGGGCTTATA AATAGTTCAG TCACCAAGTG CTTCTCTAGC AAAAATTCTC
3151 CGTTGAAGGA TTCTTTCTCT AATAGCTCAT GGGAGATAGA GGCCCAGGCA
25 3201 TTTTTTATAT TATCGGATCA GCATCCCAAC ATAATTTTAC CACACCTCAC
3251 ATTCTCAGAA GGATTGGATG AACTTTTGAA ATTGGAGGGA AATTTCCCTG
3301 AAGAAAATAA TGATAAAAAG TCTATCTATT ATTTAGGGGT CACCTCAATC
30 3351 AAAAAGAGAG AGAGTGGTGT GCTTTTGA CTGACAAGTCAA GGGTATCGTG
3401 CCCATTCCCA GCCCCCTGTT TATTCACGGA CATCAGAGTT CTCCAGGACA
35 3451 GTTGCTCACA CTTTGTAGAA AATAATATCA ACTTAGGAAC TTCTAGTAAG
3501 AAGACTTTTG CATCTTACAT GCCTCAATTC CAACTTGTT CTA CTACAGAC
3551 TCATAAGATC ATGGAAAACA AGATGTGTGA CCTAACTGTG TAATCTAGA

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Human OB Receptor Protein "D" Chromosomal DNA (Seq. ID No. 9)

5					Intron 1taccttttccag	GTG	TAC	TTC
10	CAT His 12	TGG Trp 13	G Glu 14	gtaagttatttg.....	Intron 2atatacctaacag	AA	TTT	ATT Phe Ile 15 16
15	CAA Gln 122	ATA Ile 123	G Asp 124	gtaagcatttagc.....	Intron 3ttttaaattcag	AT	GCA Ala	AAC Asn 125 126
20	TAT Tyr 163	GTT Val 164	CT Leu 165	gtaagtacaaaa.....	Intron 4ttttcaatatag	G	CCT Pro	GAA Glu 166 167
25	AAT Asn 233	ATG Met 234	G Val 235	gtaagttatgca.....	Intron 5tttttccttaag	TG	AAG Lys	CCT Pro 236 237
30	ATC Ile 281	AGA Arg 282	GAA Glu 283	gtaagtatatatt.....	Intron 6aatatttaacag	GCT Ala	GAC Asp	AAG Lys 284 285 286
35	ACA Thr 330	CAA Gln 331	G Asp 332	gtaggttatgta.....	Intron 7ccctcattacag	AT	GTC Val	ATA Ile 333 334
40	GTG Val 427	ATT Ile 428	G Asp 429	gtaagaaaacag.....	Intron 8tgtttcaaatag	AT	GTC Val	AAT Asn 430 431
45	TAT Tyr 466	CAT His 467	AG Arg 468	gtacgtattatt.....	Intron 9tatctttttaaag	G	AGC Ser	AGC Ser 469 470
50	TCT Ser 533	GTG Val 534	G Val 535	gtatgtcaagct.....	Intron 10aaaaatttctag	TG	AAG Lys	CCA Pro 536 537
55	CAA Gln 582	TGG Trp 583	AAG Lys 584	gtaccttttact.....	Intron 11cttatttttacag	ATG Met	TAT Tyr	GAG Glu 585 586 587
60	ATA Ile 636	AAA Lys 637	G Val 638	gtctgcagagat.....	Intron 12gtcattttgcag	TT	CCT Pro	ATG Met 639 640

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5	CTT TGG AAG Leu Trp Lys 663 664 665	gtattcccaatt.....	Intron 13tatttactacag	CCC CTG ATG Pro Leu Met 666 667 668
10	AGC AAA G Ser Lys Val 736 737 738	gtaagaagaggt.....	Intron 14ttttccctcag	TA AAT ATC Asn Ile 739 740
15	ATC CAT G Ile His Asp 797 798 799	gtaagtttacta.....	Intron 15ttttctcctcag	AT CAT TTT His Phe 800 801
20	ACT CAA G Thr Gln Asp 829 830 831	gtaaaaattata.....	Intron 16tttctttttcag	AT GAT ATT Asp Ile 832 833
25	CAC CAA AG His Gln Arg 864 865 866	gtattgtacttg.....	Intron 17tatecctttgtag	A ATG AAA Met Lys 867 868
30	TTT CAG AAG Phe Gln Lys 889 890 891	gttgctttttca.....	Intron 18ttatctaaacag	Exon A AGA ACG GAC Arg Thr Asp 892 893 894
35	Exon A AAA TAT GAT gtacatttgtct.....		Intron 18ctttcttttag	Exon D CCA GAA ACG Pro Glu Thr 892 893 894
40					Exon B AAA CGT TTG Lys Arg Leu 892 893 894
45	Exon D GAA ACC AGA gtatccagtggt.....		Intron 18ctttttaaacag	Exon C ATG CTT GAA Met Leu Glu 892 893 894

Human OB Receptor Protein, Recombinant Secreted Receptor amino acid sequence (Seq. ID. No. 10):

1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP
5 51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS
101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN
10 151 LFRNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD
15 251 GNLKISWSSP PLVPFFLPQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP
301 GSSYEVQVRG KRLDGPGIWS DWSTPRVETT QDVIYFPPKI LTSVGSNVSF
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK
20 401 PRGKFTYDAV YCCNEHECHH RYAEYVIDV NINISCETDG YLTGMTCRWS
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF
25 501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN
551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK
701 FTFWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN
35 751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNE GEIKWLRIS SVKKYYIHDH
801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSD

Human OB Receptor Protein, Recombinant Secreted Receptor DNA
sequence (Seq. ID. No. 11):

5 1 GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC
51 GGTCGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT
10 101 TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA
151 TAACTGCGTT TAACTTGTCA TATCCAATTA CTCCTTGGAG ATTTAAGTTG
201 TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG
15 251 GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG
301 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA
351 ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG
20 401 TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCTTTAG
451 TTTTCAACA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA
25 501 GACTTAAAAT TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT
551 CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT
601 TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTTC GATGGTTCAC
30 651 TGCAATTGCA GTGTTACGA ATGTTGTGAA TGTCTTGTC CTGTGCCAAC
701 AGCCAAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG
35 751 GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG
801 AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA
40 851 TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTCAAT
901 ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC
951 AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC
45 1001 TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT
1051 GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC
1101 TTTCCACCTA AAATTCTGAC AAGTGTGTTG TCTAATGTTT CTTTTCAGTG
50 1151 CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAGAG ATTGTTTGGT
1201 GGATGAATTT AGCTGAGAAA ATTCCTCAA GCCAGTATGA TGTTGTGAGT

1251 GATCATGTTA GCAAAGTTAC TTTTTCAT CTGAATGAAA CCAAACCTCG
5 1301 AGGAAAGTTT ACCTATGATG CAGTGACTG CTGCAATGAA CATGAATGCC
1351 ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA
1401 TGTGAAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG
10 1451 TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA
1501 GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC
1551 AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC
1601 AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC
1651 TAGGTTCACT TGACTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG
20 1701 AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG
1751 ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC
1801 AATTCCAGAT TCGCTATGGT TTAAGTGGA AAGAAGTACA ATGGAAGATG
25 1851 TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA
1901 CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC
30 1951 TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT
2001 ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA
35 2051 TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA
2101 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT
2151 TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC
40 2201 TTTCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT
2251 CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG
45 2301 AGCAAAGTAA ATATCGTGCA GTCACCTAGT GCTTATCCTT TAAACAGCAG
2351 TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT
2401 ATTTTATTAT TGAGTGAAA AATCTTAATG AAGATGGTGA AATAAAATGG
50 2451 CTTAGAATCT CTTCACTGT TAAGAAGTAT TATATCCATG ATCATTTTAT
2501 CCCCATTGAG AAGTACCAGT TCAGTCTTTA CCAATATTT ATGGAAGGAG

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2551 TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA
2601 CACCAGAGTG ATTGATAAGG ATCC

Human OB Receptor Protein, Recombinant Secreted Receptor DNA
sequence with C-terminal FLAG (Seq. ID. No. 12):

5
1 CCATTGAAGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGGATTT
51 CCAAAATGTC GTAATAACCC CGCCCCGTTG ACGCAAATGG GCGGTAGGCG
10 101 TGTACGGTGG GAGGTCTATA TAAGCAGAGC TCGTTTAGTG AACCGTCAGA
151 TCTCTAGAAG CTGGGTACCA GCTGCTAGCA AGCTTGCTAG CGGCCGCCAG
15 201 TGTGATGGAT ATCTGCAGAA TTCGGCTTTC TCTGCCTTCG GTCGAGTTGG
251 ACCCCCGGAT CAAGGTGTAC TTCTCTGAAG TAAGATGATT TGTCAAAAAT
301 TCTGTGTGGT TTTGTTACAT TGGAATTTA TTTATGTGAT AACTGCGTTT
20 351 AACTTGTCAT ATCCAATTAC TCCTTGGAGA TTTAAGTTGT CTTGCATGCC
401 ACCAAATTCA ACCTATGACT ACTTCCTTTT GCCTGCTGGG CTCTCAAAGA
25 451 ATACTTCAAA TTCGAATGGA CATTATGAGA CAGCTGTTGA ACCTAAGTTT
501 AATTCAAGTG GTACTCACTT TTCTAACTTA TCCAAAACAA CTTTCCACTG
551 TTGCTTTCGG AGTGAGCAAG ATAGAACTG CTCCTTATGT GCAGACAACA
30 601 TTGAAGGAAA GACATTTGTT TCAACAGTAA ATTCTTTAGT TTTTCAACAA
651 ATAGATGCAA ACTGGAACAT ACAGTGCTGG CTAAAAGGAG ACTTAAATTT
701 ATTCATCTGT TATGTGGAGT CATTATTTAA GAATCTATTC AGGAATTATA
35 751 ACTATAAGGT CCATCTTTTA TATGTTCTGC CTGAAGTGTT AGAAGATTCA
801 CCTCTGGTTC CCCAAAAGG CAGTTTTTCAG ATGGTTCACT GCAATTGCAG
40 851 TGTTACGAA TGTGTGAAT GTCTTGTGCC TGTGCCAACA GCCAAACTCA
901 ACGACACTCT CTTATGTGT TTGAAAATCA CATCTGGTGG AGTAATTTTC
951 CAGTCACCTC TAATGTCAGT TCAGCCCATA AATATGGTGA AGCCTGATCC
45 1001 ACCATTAGGT TTGCATATGG AAATCACAGA TGATGGTAAT TTAAAGATTT
1051 CTTGGTCCAG CCCACCATTG GTACCATTTC CACTTCAATA TCAAGTGAAA
50 1101 TATTCAGAGA ATTCTACAAC AGTTATCAGA GAAGCTGACA AGATTGTCTC
1151 AGCTACATCC CTGCTAGTAG ACAGTATACT TCCTGGGTCT TCGTATGAGG

1201 TTCAGGTGAG GGGCAAGAGA CTGGATGGCC CAGGAATCTG GAGTGACTGG
1251 AGTACTCCTC GTGTCTTTAC CACACAAGAT GTCATATACT TTCCACCTAA
5 1301 AATTCTGACA AGTGTTGGGT CTAATGTTTC TTTTCACTGC ATCTATAAGA
1351 AGGAAAACAA GATTGTTCCC TCAAAAGAGA TTGTTTGGTG GATGAATTAA
1401 GCTGAGAAAA TTCCTCAAAG CCAGTATGAT GTTGTGAGTG ATCATGTTAG
10 1451 CAAAGTTACT TTTTTCATC TGAATGAAAC CAAACCTCGA GGAAAGTTTA
1501 CCTATGATGC AGTGTACTGC TGCAATGAAC ATGAATGCCA TCATCGCTAT
1551 GCTGAATTAT ATGTGATTGA TGTCAATATC AATATCTCAT GTGAACTGA
15 1601 TGGGTACTTA ACTAAAATGA CTTGCAGATG GTCAACCAGT ACAATCCAGT
1651 CACTTGCGGA AAGCACTTTG CAATTGAGGT ATCATAGGAG CAGCCTTTAC
20 1701 TGTTCTGATA TTCCATCTAT TCATCCCATA TCTGAGCCCA AAGATTGCTA
1751 TTTGCAGAGT GATGGTTTTT ATGAATGCAT TTTCCAGCCA ATCTTCCTAT
25 1801 TATCTGGCTA CACAATGTGG ATTAGGATCA ATCACTCTCT AGGTTCACTT
1851 GACTCTCCAC CAACATGTGT CCTTCCTGAT TCTGTGGTGA AGCCACTGCC
1901 TCCATCCAGT GTGAAAGCAG AAATTACTAT AAACATTGGA TTATTGAAAA
30 1951 TATCTTGGGA AAAGCCAGTC TTTCCAGAGA ATAACCTTCA ATTCCAGATT
2001 CGCTATGGTT TAAGTGAAA AGAAGTACAA TGGAAGATGT ATGAGGTTTA
35 2051 TGATGCAAAA TCAAAATCTG TCAGTCTCCC AGTTCCAGAC TTGTGTGCAG
2101 TCTATGCTGT TCAGGTGCGC TGTAAGAGGC TAGATGGACT GGGATATTGG
2151 AGTAATTGGA GCAATCCAGC CTACACAGTT GTCATGGATA TAAAAGTTCC
40 2201 TATGAGAGGA CCTGAATTTT GGAGAATAAT TAATGGAGAT ACTATGAAAA
2251 AGGAGAAAAA TGTCACCTTA CTTTGGAAGC CCCTGATGAA AAATGACTCA
45 2301 TTGTGCAGTG TTCAGAGATA TGTGATAAAC CATCATACTT CCTGCAATGG
2351 AACATGGTCA GAAGATGTGG GAAATCACAC GAAATTCCTT TTCCTGTGGA
2401 CAGAGCAAGC ACATACTGTT ACGGTTCTGG CCATCAATTC AATTGGTGCT
50 2451 TCTGTTGCAA ATTTTAATTT AACCTTTTCA TGGCCTATGA GCAAAGTAAA
2501 TATCGTGCAG TCACTCAGTG CTTATCCTTT AAACAGCAGT TGTGTGATTG

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2551 TTTCTGGAT ACTATCACCC AGTGATTACA AGCTAATGTA TTTTATTATT
5 2601 GAGTGGAAAA ATCTTAATGA AGATGGTGAA ATAAAATGGC TTAGAATCTC
2651 TTCATCTGTT AAGAAGTATT ATATCCATGA TCATTTTATC CCCATTGAGA
2701 AGTACCAGTT CAGTCTTTAC CCAATATTTA TGGAAGGAGT GGGAAAACCA
10 2751 AAGATAATTA ATAGTTTCAC TCAAGATGAT ATTGAAAAAC ACCAGAGTGA
2801 TGCAGGTGAC TACAAGGACG ACGATGACAA GTAGGGATCC AGACATGATA
2851 AGATACATTG ATGAGTTTGG ACAACCCACA ACTAGAATGC AGTGAAAAAA
15 2901 ATGCTTTATT TGTGAAATTT GTGATGCTAT TGCTTTATTT GTAACCAT

Recombinant Human OB Receptor Protein, Natural Splice Variant
amino acid sequence (Seq. ID. No. 13)

5 1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP
51 AGLSKNTSNS NGHJETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS
10 101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLEKN
151 LFRNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV
201 PTAKLNDTLL MCLKITSGGV IFQSPILMSVQ PINMVKPDPP LGLHMEITDD
15 251 GNLKISWSSP PLVPFPLOQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP
301 GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSF
20 351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFEFLNETK
401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF
25 501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN
551 IGLLKISWEK PVFPENNLOF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK
701 FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN
35 751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNEE GEIKWLRISX SVKKYYIHGK
801 FTIL

Human OB Receptor Protein, Natural Splice Variant DNA (Seq. ID. No. 14)

1 GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC
5 51 GGTCTGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT
101 TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA
10 151 TAACTGCGTT TAACTTGTC TATCCAATTA CTCCTTGGAG ATTTAAGTTG
201 TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG
251 GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG
15 301 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA
351 ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG
20 401 TGCAGACAAC ATTGAAGGAA AGACATTGTG TTCAACAGTA AATTCTTTAG
451 TTTTTCACAA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA
501 GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT
25 551 CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT
601 TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTCA GATGGTTCAC
30 651 TGCAATTGCA GTGTTACAGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC
701 AGCCAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG
35 751 GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG
801 AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA
851 TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTCAAT
40 901 ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC
951 AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC
45 1001 TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT
1051 GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC
1101 TTTCCACCTA AAATTCTGAC AAGTGTTGGG TCTAATGTTT CTTTTCAGTG
50 1151 CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAAGAG ATTGTTTGGT
1201 GGATGAATTT AGCTGAGAAA ATTCCTCAA GCCAGTATGA TGTTGTGAGT

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1251 GATCATGTTA GCAAAGTTAC TTTTTCAT CTGAATGAAA CCAAACCTCG
1301 AGGAAAGTTT ACCTATGATG CAGTGACTG CTGCAATGAA CATGAATGCC
5 1351 ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA
1401 TGTGAAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG
1451 TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA
10 1501 GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC
1551 AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC
15 1601 AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC
1651 TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG
1701 AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG
20 1751 ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC
1801 AATTCCAGAT TCGCTATGGT TTAAGTGGAA AAGAAGTACA ATGGAAGATG
25 1851 TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA
1901 CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC
1951 TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT
30 2001 ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA
2051 TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA
35 2101 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT
2151 TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC
2201 TTTCCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT
40 2251 CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG
2301 AGCAAAGTAA ATATCGTGCA GTCACCTCAGT GCTTATCCTT TAAACAGCAG
45 2351 TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT
2401 ATTTTATTAT TGAGTGGA AATCTTAATG AAGATGGTGA AATAAAATGG
2451 CTTAGAATCT CTTATCTGT TAAGAAGTAT TATATCCATG GTAAGTTTAC
50 2501 TATACTT

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While the present invention has been described in terms of preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended
5 claims cover all such equivalent variations which come within the scope of the invention as claimed.

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SEQUENCE LISTING

5 (1) GENERAL INFORMATION:

(i) APPLICANT: CHANG, MING-SHI
WELCHER, ANDREW A.
FLETCHER, FREDERICK A.

10

(ii) TITLE OF INVENTION: OB PROTEIN RECEPTOR AND RELATED
COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 33

15

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Amgen Inc.
(B) STREET: 1840 Dehavilland Drive
(C) CITY: Thousand Oaks
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 91320

20

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

30

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Pessin, Karol M.
(C) REFERENCE/DOCKET NUMBER: A-382-A

35

40 (2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 965 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

45

(ii) MOLECULE TYPE: protein

50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

5	Met	Ile	Cys	Gln	Lys	Phe	Cys	Val	Val	Leu	Leu	His	Trp	Glu	Phe	Ile	1	5	10	15
	Tyr	Val	Ile	Thr	Ala	Phe	Asn	Leu	Ser	Tyr	Pro	Ile	Thr	Pro	Trp	Arg	20	25	30	
10	Phe	Lys	Leu	Ser	Cys	Met	Pro	Pro	Asn	Ser	Thr	Tyr	Asp	Tyr	Phe	Leu	35	40	45	
	Leu	Pro	Ala	Gly	Leu	Ser	Lys	Asn	Thr	Ser	Asn	Ser	Asn	Gly	His	Tyr	50	55	60	
15	Glu	Thr	Ala	Val	Glu	Pro	Lys	Phe	Asn	Ser	Ser	Gly	Thr	His	Phe	Ser	65	70	75	80
	Asn	Leu	Ser	Lys	Thr	Thr	Phe	His	Cys	Cys	Phe	Arg	Ser	Glu	Gln	Asp	85	90	95	
20	Arg	Asn	Cys	Ser	Leu	Cys	Ala	Asp	Asn	Ile	Glu	Gly	Lys	Thr	Phe	Val	100	105	110	
	Ser	Thr	Val	Asn	Ser	Leu	Val	Phe	Gln	Gln	Ile	Asp	Ala	Asn	Trp	Asn	115	120	125	
25	Ile	Gln	Cys	Trp	Leu	Lys	Gly	Asp	Leu	Lys	Leu	Phe	Ile	Cys	Tyr	Val	130	135	140	
30	Glu	Ser	Leu	Phe	Lys	Asn	Leu	Phe	Arg	Asn	Tyr	Asn	Tyr	Lys	Val	His	145	150	155	160
	Leu	Leu	Tyr	Val	Leu	Pro	Glu	Val	Leu	Glu	Asp	Ser	Pro	Leu	Val	Pro	165	170	175	
35	Gln	Lys	Gly	Ser	Phe	Gln	Met	Val	His	Cys	Asn	Cys	Ser	Val	His	Glu	180	185	190	
40	Cys	Cys	Glu	Cys	Leu	Val	Pro	Val	Pro	Thr	Ala	Lys	Leu	Asn	Asp	Thr	195	200	205	
	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	210	215	220	
45	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	225	230	235	240
	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	245	250	255	
50	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	260	265	270	

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Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val
 275 280 285
 5 Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr
 290 295 300
 Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser
 305 310 315 320
 10 Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe
 325 330 335
 Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys
 340 345 350
 Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp
 355 360 365
 20 Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val
 370 375 380
 Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys
 385 390 395 400
 25 Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His
 405 410 415
 Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile
 420 425 430
 30 Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg
 435 440 445
 35 Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu
 450 455 460
 Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His
 465 470 475 480
 40 Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr
 485 490 495
 Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp
 500 505 510
 45 Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys
 515 520 525
 50 Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys
 530 535 540

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Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys
 545 550 555 560
 5 Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu
 565 570 575
 Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys
 580 585 590
 10 Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala
 595 600 605
 Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn
 610 615 620
 15 Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met
 625 630 635 640
 Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys
 645 650 655
 20 Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser
 660 665 670
 Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn
 675 680 685
 Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu
 690 695 700
 30 Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile
 705 710 715 720
 Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser
 725 730 735
 35 Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser
 740 745 750
 Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met
 755 760 765
 Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys
 770 775 780
 45 Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His
 785 790 795 800
 Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met
 805 810 815
 50 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp
 820 825 830

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Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val
835 840 845

5 Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His
850 855 860

Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn
865 870 875 880

10 Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Arg Thr Asp Ile Leu
885 890 895

Ser Leu Ile Met Ile Thr Thr Asp Glu Pro Asn Val Pro Thr Ser Gln
900 905 910

Gln Ser Ile Glu Tyr Lys Ile Phe Thr Phe Arg Arg Gly Ala Asn Leu
915 920 925

20 Lys Lys Ile Gln Leu Asn Phe Glu Leu Thr Tyr Gly Gly Leu Cys Phe
930 935 940

Arg Thr Asn Arg Cys Val Asn Leu Gly Ser Lys Cys Arg Phe Glu Ser
945 950 955 960

25 Ser Leu Asp Val Leu
965

(2) INFORMATION FOR SEQ ID NO:2:

30

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3193 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

40

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

CCGCCGCCAT CTCTGCCTTC GGTGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA 60

45 GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA 120

TAAGTGCATT TAACTTGTCA TATCCAATTA CTCCTTGGAG ATTTAAGTTG TCTTGCATGC 180

50 CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA 240

ATTCGAATGG ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT 300

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	TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAACT	360
	GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCCTTAG	420
5	TTTTTCAACA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA GACTTAAAT	480
	TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG	540
	TCCATCTTTT ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCCAAAAG	600
10	GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTCATGA ATGTTGTGAA TGTCTTGTGC	660
	CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG	720
15	GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCCAT AAATATGGTG AAGCCTGATC	780
	CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA TTTAAAGATT TCTTGGTCCA	840
	GCCCACCATT GGTACCATT CCACCTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA	900
20	CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC	960
	TTCTGTTGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT	1020
25	GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC TTTCCACCTA	1080
	AAATTCTGAC AAGTGTGGG TCTAATGTTT CTTTTCAGTG CATCTATAAG AAGGAAAACA	1140
	AGATTGTTCC CTCAAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAAA	1200
30	GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT CTGAATGAAA	1260
	CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGTACTG CTGCAATGAA CATGAATGCC	1320
35	ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA TGTGAACTG	1380
	ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG	1440
	AAAGCACTTT GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA	1500
40	TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA	1560
	TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC	1620
45	TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG AAGCCACTGC	1680
	CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG	1740
	AAAAGCCAGT CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGAA	1800
50	AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC	1860
	CAGTTCCAGA CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC	1920

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	TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT ATAAAAGTTC	1980
5	CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA	2040
	ATGTCACTTT ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT	2100
	ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA	2160
10	CGAAATTCAC TTTCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT	2220
	CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG AGCAAAGTAA	2280
15	ATATCGTGCA GTCACCTCAGT GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA	2340
	TACTATCACC CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAT AATCTTAATG	2400
	AAGATGGTGA AATAAAATGG CTTAGAATCT CTTTCATCTGT TAAGAAGTAT TATATCCATG	2460
20	ATCATTTTAT CCCCATGAG AAGTACCAGT TCAGTCTTTA CCCAATATTT ATGGAAGGAG	2520
	TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA CACCAGAGTG	2580
25	ATGCAGGTTT ATATGTAATT GTGCCAGTAA TTATTTCTCTC TTCCATCTTA TTGCTTGGA	2640
	CATTATTAAT ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA	2700
	AGAATTGTTC CTGGGCACAA GGAATTAATT TTCAGAAGAG AACGGACATT CTTTGAAGTC	2760
30	TAATCATGAT CACTACAGAT GAACCCAATG TGCCAACTTC CCAACAGTCT ATAGAGTATT	2820
	AGAAGATTTT TACATTTTGA AGAAGGGGAG CAAATCTAAA AAAAATTCAG TTGAACTTCT	2880
35	GAGAGTTAAC ATATGGTGGA TTATGTTGAT TTAGAACTTA AAATAGATGT GTAAATTTGG	2940
	GTTCAAAATG TAGATTTGAG TCCAGTTTGG ATGTGTGATT AATTTTCAA TCATCTAAAG	3000
	TTTAAAAGTA GTATTCATGA TTTCTGGCTT TTGATTTGCC ATATTCCTGG TCATAAAACA	3060
40	TTAAGAAAAT TATGGCTGTT GCTGTCATTA CATATCTATT AAATGTCATC AAATATGTAG	3120
	TAGACAATTT TGTAATTAGG TGAACCTTAA AACTGCAACA TCTGACAAAT TGCTTTAAAA	3180
45	ATACAATGAT TAT	3193

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 995 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- 100 -

(ii) MOLECULE TYPE: protein

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

1	Met	Ile	Cys	Gln	Lys	Phe	Cys	Val	Val	Leu	Leu	His	Trp	Glu	Phe	Ile	
					5					10					15		
10	Tyr	Val	Ile	Thr	Ala	Phe	Asn	Leu	Ser	Tyr	Pro	Ile	Thr	Pro	Trp	Arg	
				20					25					30			
15	Phe	Lys	Leu	Ser	Cys	Met	Pro	Pro	Asn	Ser	Thr	Tyr	Asp	Tyr	Phe	Leu	
			35					40					45				
	Leu	Pro	Ala	Gly	Leu	Ser	Lys	Asn	Thr	Ser	Asn	Ser	Asn	Gly	His	Tyr	
		50					55					60					
20	Glu	Thr	Ala	Val	Glu	Pro	Lys	Phe	Asn	Ser	Ser	Gly	Thr	His	Phe	Ser	
	65					70					75					80	
	Asn	Leu	Ser	Lys	Thr	Thr	Phe	His	Cys	Cys	Phe	Arg	Ser	Glu	Gln	Asp	
				85						90					95		
25	Arg	Asn	Cys	Ser	Leu	Cys	Ala	Asp	Asn	Ile	Glu	Gly	Lys	Thr	Phe	Val	
			100						105					110			
	Ser	Thr	Val	Asn	Ser	Leu	Val	Phe	Gln	Gln	Ile	Asp	Ala	Asn	Trp	Asn	
30			115					120					125				
	Ile	Gln	Cys	Trp	Leu	Lys	Gly	Asp	Leu	Lys	Leu	Phe	Ile	Cys	Tyr	Val	
		130					135					140					
35	Glu	Ser	Leu	Phe	Lys	Asn	Leu	Phe	Arg	Asn	Tyr	Asn	Tyr	Lys	Val	His	
	145					150					155					160	
	Leu	Leu	Tyr	Val	Leu	Pro	Glu	Val	Leu	Glu	Asp	Ser	Pro	Leu	Val	Pro	
				165						170					175		
40	Gln	Lys	Gly	Ser	Phe	Gln	Met	Val	His	Cys	Asn	Cys	Ser	Val	His	Glu	
				180					185					190			
	Cys	Cys	Glu	Cys	Leu	Val	Pro	Val	Pro	Thr	Ala	Lys	Leu	Asn	Asp	Thr	
45			195				200						205				
	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	
		210					215					220					
50	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	
	225					230					235					240	

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	Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser	245	250	255
5	Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys	260	265	270
	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	275	280	285
10	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	290	295	300
	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	305	310	320
15	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	325	330	335
	Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys	340	345	350
20	Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp	355	360	365
	Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val	370	375	380
25	Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys	385	390	395
30	Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His	405	410	415
	Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile	420	425	430
35	Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg	435	440	445
	Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu	450	455	460
40	Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His	465	470	475
45	Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr	485	490	495
	Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp	500	505	510
50	Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys	515	520	525

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	Val	Leu	Pro	Asp	Ser	Val	Val	Lys	Pro	Leu	Pro	Pro	Ser	Ser	Val	Lys	
	530							535				540					
5	Ala	Glu	Ile	Thr	Ile	Asn	Ile	Gly	Leu	Leu	Lys	Ile	Ser	Trp	Glu	Lys	
	545					550					555					560	
	Pro	Val	Phe	Pro	Glu	Asn	Asn	Leu	Gln	Phe	Gln	Ile	Arg	Tyr	Gly	Leu	
					565					570					575		
10	Ser	Gly	Lys	Glu	Val	Gln	Trp	Lys	Met	Tyr	Glu	Val	Tyr	Asp	Ala	Lys	
				580					585					590			
	Ser	Lys	Ser	Val	Ser	Leu	Pro	Val	Pro	Asp	Leu	Cys	Ala	Val	Tyr	Ala	
15				595				600					605				
	Val	Gln	Val	Arg	Cys	Lys	Arg	Leu	Asp	Gly	Leu	Gly	Tyr	Trp	Ser	Asn	
	610						615					620					
20	Trp	Ser	Asn	Pro	Ala	Tyr	Thr	Val	Val	Met	Asp	Ile	Lys	Val	Pro	Met	
	625					630					635					640	
	Arg	Gly	Pro	Glu	Phe	Trp	Arg	Ile	Ile	Asn	Gly	Asp	Thr	Met	Lys	Lys	
					645					650					655		
25	Glu	Lys	Asn	Val	Thr	Leu	Leu	Trp	Lys	Pro	Leu	Met	Lys	Asn	Asp	Ser	
				660					665					670			
	Leu	Cys	Ser	Val	Gln	Arg	Tyr	Val	Ile	Asn	His	His	Thr	Ser	Cys	Asn	
30				675				680					685				
	Gly	Thr	Trp	Ser	Glu	Asp	Val	Gly	Asn	His	Thr	Lys	Phe	Thr	Phe	Leu	
	690					695						700					
35	Trp	Thr	Glu	Gln	Ala	His	Thr	Val	Thr	Val	Leu	Ala	Ile	Asn	Ser	Ile	
	705					710					715					720	
	Gly	Ala	Ser	Val	Ala	Asn	Phe	Asn	Leu	Thr	Phe	Ser	Trp	Pro	Met	Ser	
					725					730					735		
40	Lys	Val	Asn	Ile	Val	Gln	Ser	Leu	Ser	Ala	Tyr	Pro	Leu	Asn	Ser	Ser	
				740					745					750			
	Cys	Val	Ile	Val	Ser	Trp	Ile	Leu	Ser	Pro	Ser	Asp	Tyr	Lys	Leu	Met	
45				755				760					765				
	Tyr	Phe	Ile	Ile	Glu	Trp	Lys	Asn	Leu	Asn	Glu	Asp	Gly	Glu	Ile	Lys	
	770						775					780					
50	Trp	Leu	Arg	Ile	Ser	Ser	Ser	Val	Lys	Lys	Tyr	Tyr	Ile	His	Asp	His	
	785					790					795					800	

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Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met
 805 810 815
 5 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp
 820 825 830
 Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val
 835 840 845
 10 Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His
 850 855 860
 Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn
 865 870 875 880
 15 Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Lys Arg Leu Ser Ile
 885 890 895
 Phe Leu Ser Ser Ile Gln His Gln His Val Val Leu Phe Phe Trp Ser
 900 905 910
 20 Leu Lys Gln Phe Gln Lys Ile Ser Val Leu Ile His His Gly Lys Ile
 915 920 925
 25 Lys Met Arg Cys Gln Gln Leu Trp Ser Leu Tyr Phe Gln Gln Gln Ile
 930 935 940
 Leu Lys Arg Val Leu Phe Val Leu Val Thr Ser Ser Thr Val Leu Thr
 945 950 955 960
 30 Ser Leu Arg Leu Arg Val Leu Arg Pro Met Arg Thr Lys Ala Arg Asp
 965 970 975
 35 Asn Pro Leu Leu Asn Thr Pro Arg Ser Ala Thr Leu Asn Gln Val Lys
 980 985 990
 Leu Val Lys
 995

40 (2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 3063 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

	CCGCCGCCAT CTCTGCCTTC GGTCGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA	60
5	GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA	120
	TAACTGCGTT TAACTTGTC A TATCCAATTA CTCCTTGGAG ATTTAAGTTG TCTTGCATGC	180
	CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA	240
10	ATTCGAATGG ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT	300
	TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAAACT	360
15	GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCTTTAG	420
	TTTTTCAACA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA GACTTAAAT	480
	TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG	540
20	TCCATCTTTT ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCCAAAAG	600
	GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTCATGA ATGTTGTGAA TGTCTGTGC	660
25	CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG	720
	GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG AAGCCTGATC	780
	CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA TTTAAAGATT TCTTGGTCCA	840
30	GCCCACCATT GGTACCATT CCACCTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA	900
	CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC	960
35	TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT	1020
	GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC TTTCCACCTA	1080
	AAATTCTGAC AAGTGTGGG TCTAATGTTT CTTTTCCTG CATCTATAAG AAGGAAAACA	1140
40	AGATTGTTCC CTCAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAA	1200
	GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT CTGAATGAAA	1260
45	CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGACTG CTGCAATGAA CATGAATGCC	1320
	ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA TGTGAACTG	1380
	ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG	1440
50	AAAGCACTTT GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA	1500
	TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA	1560

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	TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC	1620
5	TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG AAGCCACTGC	1680
	CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG	1740
	AAAAGCCAGT CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGA	1800
10	AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC	1860
	CAGTTCAGAG CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC	1920
15	TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT ATAAAAGTTC	1980
	CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA	2040
	ATGTCACTTT ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT	2100
20	ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA	2160
	CGAAATTCAC TTTCCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT	2220
25	CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG AGCAAAGTAA	2280
	ATATCGTGCA GTCACCTCAGT GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA	2340
	TACTATCACC CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAG AATCTTAATG	2400
30	AAGATGGTGA AATAAAATGG CTTAGAATCT CTTTCATCTGT TAAGAAGTAT TATATCCATG	2460
	ATCATTTTAT CCCCATTGAG AAGTACCAGT TCAGTCTTTA CCCAATATTT ATGGAAGGAG	2520
35	TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA CACCAGAGTG	2580
	ATGCAGGTTT ATATGTAATT GTGCCAGTAA TTATTTCTCTC TTCCATCTTA TTGCTTGGA	2640
	CATTATTAAT ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA	2700
40	AGAATTGTTC CTGGGCACAA GGACTTAATT TTCAGAAGAA ACGTTTGAGC ATCTTTTAT	2760
	CAAGCATACA GCATCAGTGA CATGTGGTCC TCTTCTTTTG GAGCCTGAAA CAATTTTCA	2820
45	AGATATCAGT GTTGATACAT CATGGAAAAA TAAAGATGAG ATGATGCCAA CAACTGTGGT	2880
	CTCTCTACTT TCAACAACAG ATCTTGAAAA GGGTTCTGTT TGTTTTAGTG ACCAGTTCAA	2940
	CAGTGTTAAC TTCTCTGAGG CTGAGGGTAC TGAGGTAACC TATGAGGACG AAAGCCAGAG	3000
50	ACAACCCTTT GTTAAATACG CCACGCTGAT CAGCAACTCT AAACCAAGTG AAAGTGGTGA	3060
	AGA	3063

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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 969 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile
 1 5 10 15
 Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg
 20 25 30
 Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu
 35 40 45
 Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr
 50 55 60
 Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser
 65 70 75 80
 Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp
 85 90 95
 Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val
 100 105 110
 Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn
 115 120 125
 Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val
 130 135 140
 Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His
 145 150 155 160
 Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro
 165 170 175
 Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu
 180 185 190
 Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr
 195 200 205

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5 Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser
 210 215 220
 Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro
 225 230 235 240
 10 Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser
 245 250 255
 Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys
 260 265 270
 15 Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val
 275 280 285
 Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr
 290 295 300
 20 Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser
 305 310 315 320
 Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe
 325 330 335
 25 Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys
 340 345 350
 30 Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp
 355 360 365
 Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val
 370 375 380
 35 Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys
 385 390 395 400
 40 Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His
 405 410 415
 Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile
 420 425 430
 45 Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg
 435 440 445
 Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu
 450 455 460
 50 Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His
 465 470 475 480

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Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr
 485 490 495
 5 Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp
 500 505 510
 Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys
 515 520 525
 10 Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys
 530 535 540
 Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys
 545 550 555 560
 15 Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu
 565 570 575
 Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys
 580 585 590
 20 Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala
 595 600 605
 25 Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn
 610 615 620
 Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met
 625 630 635 640
 30 Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys
 645 650 655
 Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser
 660 665 670
 35 Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn
 675 680 685
 40 Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu
 690 695 700
 Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile
 705 710 715 720
 45 Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser
 725 730 735
 Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser
 740 745 750
 50 Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met
 755 760 765

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Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys
 770 775 780
 5 Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His
 785 790 795 800
 Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met
 805 810 815
 10 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp
 820 825 830
 Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val
 835 840 845
 15 Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His
 850 855 860
 20 Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn
 865 870 875 880
 Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Met Leu Glu Gly Ser
 885 890 895
 25 Met Phe Val Lys Ser His His His Ser Leu Ile Ser Ser Thr Gln Gly
 900 905 910
 His Lys His Cys Gly Arg Pro Gln Gly Pro Leu His Arg Lys Thr Arg
 915 920 925
 Asp Leu Cys Ser Leu Val Tyr Leu Leu Thr Leu Pro Pro Leu Leu Ser
 930 935 940
 35 Tyr Asp Pro Ala Lys Ser Pro Ser Val Arg Asn Thr Gln Glu Ser Ile
 945 950 955 960
 Lys Lys Lys Lys Lys Lys Leu Glu Gly
 965
 40

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- 45 (A) LENGTH: 969 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

5	Met	Ile	Cys	Gln	Lys	Phe	Cys	Val	Val	Leu	Leu	His	Trp	Glu	Phe	Ile	1	5	10	15
10	Tyr	Val	Ile	Thr	Ala	Phe	Asn	Leu	Ser	Tyr	Pro	Ile	Thr	Pro	Trp	Arg	20	25	30	
15	Phe	Lys	Leu	Ser	Cys	Met	Pro	Pro	Asn	Ser	Thr	Tyr	Asp	Tyr	Phe	Leu	35	40	45	
20	Leu	Pro	Ala	Gly	Leu	Ser	Lys	Asn	Thr	Ser	Asn	Ser	Asn	Gly	His	Tyr	50	55	60	
25	Glu	Thr	Ala	Val	Glu	Pro	Lys	Phe	Asn	Ser	Ser	Gly	Thr	His	Phe	Ser	65	70	75	80
30	Asn	Leu	Ser	Lys	Thr	Thr	Phe	His	Cys	Cys	Phe	Arg	Ser	Glu	Gln	Asp	85	90	95	
35	Arg	Asn	Cys	Ser	Leu	Cys	Ala	Asp	Asn	Ile	Glu	Gly	Lys	Thr	Phe	Val	100	105	110	
40	Ser	Thr	Val	Asn	Ser	Leu	Val	Phe	Gln	Gln	Ile	Asp	Ala	Asn	Trp	Asn	115	120	125	
45	Ile	Gln	Cys	Trp	Leu	Lys	Gly	Asp	Leu	Lys	Leu	Phe	Ile	Cys	Tyr	Val	130	135	140	
50	Glu	Ser	Leu	Phe	Lys	Asn	Leu	Phe	Arg	Asn	Tyr	Asn	Tyr	Lys	Val	His	145	150	155	160
55	Leu	Leu	Tyr	Val	Leu	Pro	Glu	Val	Leu	Glu	Asp	Ser	Pro	Leu	Val	Pro	165	170	175	
60	Gln	Lys	Gly	Ser	Phe	Gln	Met	Val	His	Cys	Asn	Cys	Ser	Val	His	Glu	180	185	190	
65	Cys	Cys	Glu	Cys	Leu	Val	Pro	Val	Pro	Thr	Ala	Lys	Leu	Asn	Asp	Thr	195	200	205	
70	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	210	215	220	
75	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	225	230	235	240
80	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	245	250	255	
85	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	260	265	270	

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	Tyr	Ser	Glu	Asn	Ser	Thr	Thr	Val	Ile	Arg	Glu	Ala	Asp	Lys	Ile	Val	
			275					280					285				
5	Ser	Ala	Thr	Ser	Leu	Leu	Val	Asp	Ser	Ile	Leu	Pro	Gly	Ser	Ser	Tyr	
		290					295					300					
	Glu	Val	Gln	Val	Arg	Gly	Lys	Arg	Leu	Asp	Gly	Pro	Gly	Ile	Trp	Ser	
	305					310					315					320	
10	Asp	Trp	Ser	Thr	Pro	Arg	Val	Phe	Thr	Thr	Gln	Asp	Val	Ile	Tyr	Phe	
					325					330					335		
	Pro	Pro	Lys	Ile	Leu	Thr	Ser	Val	Gly	Ser	Asn	Val	Ser	Phe	His	Cys	
15				340					345					350			
	Ile	Tyr	Lys	Lys	Glu	Asn	Lys	Ile	Val	Pro	Ser	Lys	Glu	Ile	Val	Trp	
			355					360					365				
20	Trp	Met	Asn	Leu	Ala	Glu	Lys	Ile	Pro	Gln	Ser	Gln	Tyr	Asp	Val	Val	
	370						375					380					
	Ser	Asp	His	Val	Ser	Lys	Val	Thr	Phe	Phe	Asn	Leu	Asn	Glu	Thr	Lys	
	385					390					395					400	
25	Pro	Arg	Gly	Lys	Phe	Thr	Tyr	Asp	Ala	Val	Tyr	Cys	Cys	Asn	Glu	His	
				405						410					415		
	Glu	Cys	His	His	Arg	Tyr	Ala	Glu	Leu	Tyr	Val	Ile	Asp	Val	Asn	Ile	
30				420					425					430			
	Asn	Ile	Ser	Cys	Glu	Thr	Asp	Gly	Tyr	Leu	Thr	Lys	Met	Thr	Cys	Arg	
			435					440					445				
35	Trp	Ser	Thr	Ser	Thr	Ile	Gln	Ser	Leu	Ala	Glu	Ser	Thr	Leu	Gln	Leu	
	450						455					460					
	Arg	Tyr	His	Arg	Ser	Ser	Leu	Tyr	Cys	Ser	Asp	Ile	Pro	Ser	Ile	His	
	465					470					475					480	
40	Pro	Ile	Ser	Glu	Pro	Lys	Asp	Cys	Tyr	Leu	Gln	Ser	Asp	Gly	Phe	Tyr	
				485						490					495		
	Glu	Cys	Ile	Phe	Gln	Pro	Ile	Phe	Leu	Leu	Ser	Gly	Tyr	Thr	Met	Trp	
45				500					505					510			
	Ile	Arg	Ile	Asn	His	Ser	Leu	Gly	Ser	Leu	Asp	Ser	Pro	Pro	Thr	Cys	
			515					520					525				
50	Val	Leu	Pro	Asp	Ser	Val	Val	Lys	Pro	Leu	Pro	Pro	Ser	Ser	Val	Lys	
	530						535					540					
	Ala	Glu	Ile	Thr	Ile	Asn	Ile	Gly	Leu	Leu	Lys	Ile	Ser	Trp	Glu	Lys	
	545					550					555					560	

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	Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu	565	570	575
5	Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys	580	585	590
	Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala	595	600	605
10	Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn	610	615	620
	Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met	625	630	635
15	Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys	645	650	655
	Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser	660	665	670
20	Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn	675	680	685
	Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu	690	695	700
25	Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile	705	710	715
30	Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser	725	730	735
	Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser	740	745	750
35	Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met	755	760	765
40	Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys	770	775	780
	Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His	785	790	795
45	Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met	805	810	815
50	Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp	820	825	830

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Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val
835 840 845

Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His
850 855 860

Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn
865 870 875 880

Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Met Leu Glu Gly Ser
885 890 895

Met Phe Val Lys Ser His His His Ser Leu Ile Ser Ser Thr Gln Gly
900 905 910

His Lys His Cys Gly Arg Pro Gln Gly Pro Leu His Arg Lys Thr Arg
915 920 925

Asp Leu Cys Ser Leu Val Tyr Leu Leu Thr Leu Pro Pro Leu Leu Ser
930 935 940

Tyr Asp Pro Ala Lys Ser Pro Ser Val Arg Asn Thr Gln Glu Ser Ile
945 950 955 960

Lys Lys Lys Lys Lys Lys Leu Glu Gly
965

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1216 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile
1 5 10 15

Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg
20 25 30

Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu
35 40 45

Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr
50 55 60

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	Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser	65	70	75	80
5	Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp	85	90	95	
	Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val	100	105	110	
10	Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn	115	120	125	
	Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val	130	135	140	
15	Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His	145	150	155	160
20	Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro	165	170	175	
	Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu	180	185	190	
25	Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr	195	200	205	
	Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser	210	215	220	
30	Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro	225	230	235	240
	Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser	245	250	255	
35	Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys	260	265	270	
40	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	275	280	285	
	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	290	295	300	
45	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	305	310	315	320
50	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	325	330	335	

[illegible]

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	Trp	Ser	Asn	Pro	Ala	Tyr	Thr	Val	Val	Met	Asp	Ile	Lys	Val	Pro	Met	
	625					630					635					640	
5	Arg	Gly	Pro	Glu	Phe	Trp	Arg	Ile	Ile	Asn	Gly	Asp	Thr	Met	Lys	Lys	
					645					650					655		
	Glu	Lys	Asn	Val	Thr	Leu	Leu	Trp	Lys	Pro	Leu	Met	Lys	Asn	Asp	Ser	
				660					665					670			
10	Leu	Cys	Ser	Val	Gln	Arg	Tyr	Val	Ile	Asn	His	His	Thr	Ser	Cys	Asn	
			675					680					685				
	Gly	Thr	Trp	Ser	Glu	Asp	Val	Gly	Asn	His	Thr	Lys	Phe	Thr	Phe	Leu	
15			690				695					700					
	Trp	Thr	Glu	Gln	Ala	His	Thr	Val	Thr	Val	Leu	Ala	Ile	Asn	Ser	Ile	
	705				710						715					720	
20	Gly	Ala	Ser	Val	Ala	Asn	Phe	Asn	Leu	Thr	Phe	Ser	Trp	Pro	Met	Ser	
					725					730					735		
	Lys	Val	Asn	Ile	Val	Gln	Ser	Leu	Ser	Ala	Tyr	Pro	Leu	Asn	Ser	Ser	
				740					745					750			
25	Cys	Val	Ile	Val	Ser	Trp	Ile	Leu	Ser	Pro	Ser	Asp	Tyr	Lys	Leu	Met	
			755					760					765				
	Tyr	Phe	Ile	Ile	Glu	Trp	Lys	Asn	Leu	Asn	Glu	Asp	Gly	Glu	Ile	Lys	
30			770				775					780					
	Trp	Leu	Arg	Ile	Ser	Ser	Ser	Val	Lys	Lys	Tyr	Tyr	Ile	His	Asp	His	
	785					790					795					800	
35	Phe	Ile	Pro	Ile	Glu	Lys	Tyr	Gln	Phe	Ser	Leu	Tyr	Pro	Ile	Phe	Met	
				805						810					815		
	Glu	Gly	Val	Gly	Lys	Pro	Lys	Ile	Ile	Asn	Ser	Phe	Thr	Gln	Asp	Asp	
				820					825					830			
40	Ile	Glu	Lys	His	Gln	Ser	Asp	Ala	Gly	Leu	Tyr	Val	Ile	Val	Pro	Val	
			835					840					845				
	Ile	Ile	Ser	Ser	Ser	Ile	Leu	Leu	Leu	Gly	Thr	Leu	Leu	Ile	Ser	His	
45			850				855					860					
	Gln	Arg	Met	Lys	Lys	Leu	Phe	Trp	Glu	Asp	Val	Pro	Asn	Pro	Lys	Asn	
	865					870				875						880	
50	Cys	Ser	Trp	Ala	Gln	Gly	Leu	Asn	Phe	Gln	Lys	Pro	Glu	Thr	Phe	Glu	
				885						890					895		

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	His	Leu	Phe	Ile	Lys	His	Thr	Ala	Ser	Val	Thr	Cys	Gly	Pro	Leu	Leu	
				900					905					910			
5	Leu	Glu	Pro	Glu	Thr	Ile	Ser	Glu	Asp	Ile	Ser	Val	Asp	Thr	Ser	Trp	
			915					920					925				
	Lys	Asn	Lys	Asp	Glu	Met	Met	Pro	Thr	Thr	Val	Val	Ser	Leu	Leu	Ser	
		930					935					940					
10	Thr	Thr	Asp	Leu	Glu	Lys	Gly	Ser	Val	Cys	Ile	Ser	Asp	Gln	Phe	Asn	
	945					950					955					960	
	Ser	Val	Asn	Phe	Ser	Glu	Ala	Glu	Gly	Thr	Glu	Val	Thr	Tyr	Glu	Asp	
					965					970						975	
15	Glu	Ser	Gln	Arg	Gln	Pro	Phe	Val	Lys	Tyr	Ala	Thr	Leu	Ile	Ser	Asn	
				980					985					990			
	Ser	Lys	Pro	Ser	Glu	Thr	Gly	Glu	Glu	Gln	Gly	Leu	Ile	Asn	Ser	Ser	
20			995					1000					1005				
	Val	Thr	Lys	Cys	Phe	Ser	Ser	Lys	Asn	Ser	Pro	Leu	Lys	Asp	Ser	Phe	
		1010					1015					1020					
25	Ser	Asn	Ser	Ser	Trp	Glu	Ile	Glu	Ala	Gln	Ala	Phe	Phe	Ile	Leu	Ser	
	1025					1030					1035					1040	
	Asp	Gln	His	Pro	Asn	Ile	Ile	Ser	Pro	His	Leu	Thr	Phe	Ser	Glu	Gly	
					1045					1050					1055		
30	Leu	Asp	Glu	Leu	Leu	Lys	Leu	Glu	Gly	Asn	Phe	Pro	Glu	Glu	Asn	Asn	
				1060					1065					1070			
	Asp	Lys	Lys	Ser	Ile	Tyr	Tyr	Leu	Gly	Val	Thr	Ser	Ile	Lys	Lys	Arg	
35			1075					1080					1085				
	Glu	Ser	Gly	Val	Leu	Leu	Thr	Asp	Lys	Ser	Arg	Val	Ser	Cys	Pro	Phe	
		1090					1095					1100					
40	Pro	Ala	Pro	Cys	Leu	Phe	Thr	Asp	Ile	Arg	Val	Leu	Gln	Asp	Ser	Cys	
	1105					1110					1115					1120	
	Ser	His	Phe	Val	Glu	Asn	Asn	Ile	Asn	Leu	Gly	Thr	Ser	Ser	Lys	Lys	
					1125					1130					1135		
45	Thr	Phe	Ala	Ser	Tyr	Met	Pro	Gln	Phe	Gln	Thr	Cys	Ser	Thr	Gln	Thr	
				1140					1145					1150			
	His	Lys	Ile	Met	Glu	Asn	Lys	Met	Cys	Asp	Leu	Thr	Val	Phe	His	Arg	
50			1155					1160					1165				
	Asn	Leu	Gln	Ile	Cys	Val	Ile	Met	Gly	Asn	Ile	Lys	Cys	Asn	Arg	Leu	
		1170					1175					1180					

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Leu Trp Val Gly Glu Arg Lys Glu Thr Arg Val Lys Phe Glu Asn Asn
 1185 1190 1195 1200

5 Cys Ser Lys Lys Lys Lys Lys Asn Ser Arg Pro Ala Arg Pro Asp
 1205 1210 1215

(2) INFORMATION FOR SEQ ID NO:8:

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3599 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

25 GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC GGTCGAGTTG 60
 GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG 120
 TTTTGTTACA TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTC AATCCAATTA 180
 30 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT 240
 TGCCTGCTGG GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG 300
 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA ACTTTCCACT 360
 35 GTTGCTTTTCG GAGTGAGCAA GATAGAACT GTCCTTATG TGCAGACAAC ATTGAAGGAA 420
 AGACATTTGT TTCAACAGTA AATTCTTTAG TTTTCAACA AATAGATGCA AACTGGAACA 480
 40 TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA 540
 AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT 600
 TAGAAGATTC ACCTCTGGTT CCCCAAAAAG GCAGTTTCA GATGGTTCAC TGCAATTGCA 660
 45 GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC 720
 TCCTTATGTG TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG 780
 50 TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTGTCATATG GAAATCACAG 840
 ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTCAAT 900

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	ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC AAGATTGTCT	960
	CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA	1020
5	GGGGCAAGAG ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA	1080
	CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG TCTAATGTTT	1140
	CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAAGAG ATTGTTTGGT	1200
10	GGATGAATTT AGCTGAGAAA ATTCCTCAAA GCCAGTATGA TGTTGTGAGT GATCATGTTA	1260
	GCAAAGTTAC TTTTTTCAAT CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG	1320
15	CAGTGTACTG CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG	1380
	ATGTCAATAT CAATATCTCA TGTGAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT	1440
	GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA	1500
20	GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC AAAGATTGCT	1560
	ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTCCAGCC AATCTTCCTA TTATCTGGCT	1620
25	ACACAATGTG GATTAGGATC AATCACTCTC TAGGTTCACT TGA CTCTCCA CCAACATGTG	1680
	TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA	1740
	TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCAGAG AATAACCTTC	1800
30	AATTCCAGAT TCGCTATGGT TTAAGTGGAA AAGAAGTACA ATGGAAGATG TATGAGGTTT	1860
	ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCAGA CTTGTGTGCA GTCTATGCTG	1920
35	TTCAGGTGCG CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG	1980
	CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA	2040
	TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACCTT ACTTTGGAAG CCCCTGATGA	2100
40	AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT TCCTGCAATG	2160
	GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG	2220
45	CACATACTGT TACGGTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT	2280
	TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT GCTTATCCTT	2340
	TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT	2400
50	ATTTTATTAT TGAGTGGAAG AATCTTAATG AAGATGGTGA AATAAAATGG CTTAGAATCT	2460
	CTTCATCTGT TAAGAAGTAT TATATCCATG ATCATTTTAT CCCCATGAG AAGTACCAGT	2520

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TCAGTCTTTA CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA 2580
CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT GTGCCAGTAA 2640
5 TTATTTCTCTC TTCCATCTTA TTGCTTGGAA CATTATTAAT ATCACACCAA AGAATGAAAA 2700
AGCTATTTTG GGAAGATGTT CCGAACCCCA AGAATTGTTC CTGGGCACAA GGACTTAATT 2760
10 TTCAGAAGCC AGAAACGTTT GAGCATCTTT TTATCAAGCA TACAGCATCA GTGACATGTG 2820
GTCCTCTTCT TTTGGAGCCT GAAACAATTT CAGAAGATAT CAGTGTTGAT ACATCATGGA 2880
AAAATAAAGA TGAGATGATG CCAACAACCTG TGGTCTCTCT ACTTTCAACA ACAGATCTTG 2940
15 AAAAGGGTTC TGTTTGTATT AGTGACCAGT TCAACAGTGT TAACTTCTCT GAGGCTGAGG 3000
GTACTGAGGT AACCTATGAG GACGAAAGCC AGAGACAACC CTTTGTTAA TACGCCACGC 3060
20 TGATCAGCAA CTCTAAACCA AGTGAAACTG GTGAAGAACA AGGGCTTATA AATAGTTCAG 3120
TCACCAAGTG CTTCTCTAGC AAAAATTCTC CGTTGAAGGA TTCTTTCTCT AATAGCTCAT 3180
GGGAGATAGA GGCCCAGGCA TTTTTTATAT TATCGGATCA GCATCCCAAC ATAATTTAC 3240
25 CACACCTCAC ATTCTCAGAA GGATTGGATG AACTTTTGAA ATTGGAGGGA AATTTCCCTG 3300
AAGAAAATAA TGATAAAAAG TCTATCTATT ATTTAGGGGT CACCTCAATC AAAAAGAGAG 3360
30 AGAGTGGTGT GCTTTTGACT GACAAGTCAA GGGTATCGTG CCCATTCCCA GCCCCCTGTT 3420
TATTCACGGA CATCAGAGTT CTCCAGGACA GTTGCTCACA CTTTGTAGAA AATAATATCA 3480
ACTTAGGAAC TTCTAGTAAG AAGACTTTTG CATCTTACAT GCCTCAATTC CAAACTTGTT 3540
35 CTACTCAGAC TCATAAGATC ATGGAAAACA AGATGTGTGA CCTAACTGTG TAATCTAGA 3599

(2) INFORMATION FOR SEQ ID NO:9:

40 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: cDNA

50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

NNNNNTACCT TTTCCAG

17

5 (2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 839 amino acids

(B) TYPE: amino acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

20 Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile
1 5 10 15

Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg
20 25 30

25 Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu
35 40 45

30 Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr
50 55 60

Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser
65 70 75 80

35 Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp
85 90 95

40 Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val
100 105 110

Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn
115 120 125

45 Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val
130 135 140

Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His
145 150 155 160

50 Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro
165 170 175

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	Gln	Lys	Gly	Ser	Phe	Gln	Met	Val	His	Cys	Asn	Cys	Ser	Val	His	Glu	
				180					185					190			
5	Cys	Cys	Glu	Cys	Leu	Val	Pro	Val	Pro	Thr	Ala	Lys	Leu	Asn	Asp	Thr	
			195					200					205				
	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	
		210					215					220					
10	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	
	225					230					235					240	
	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	
				245					250						255		
15	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	
				260					265					270			
	Tyr	Ser	Glu	Asn	Ser	Thr	Thr	Val	Ile	Arg	Glu	Ala	Asp	Lys	Ile	Val	
20			275					280					285				
	Ser	Ala	Thr	Ser	Leu	Leu	Val	Asp	Ser	Ile	Leu	Pro	Gly	Ser	Ser	Tyr	
		290					295					300					
25	Glu	Val	Gln	Val	Arg	Gly	Lys	Arg	Leu	Asp	Gly	Pro	Gly	Ile	Trp	Ser	
	305					310					315					320	
	Asp	Trp	Ser	Thr	Pro	Arg	Val	Phe	Thr	Thr	Gln	Asp	Val	Ile	Tyr	Phe	
				325					330						335		
30	Pro	Pro	Lys	Ile	Leu	Thr	Ser	Val	Gly	Ser	Asn	Val	Ser	Phe	His	Cys	
			340						345					350			
	Ile	Tyr	Lys	Lys	Glu	Asn	Lys	Ile	Val	Pro	Ser	Lys	Glu	Ile	Val	Trp	
35			355					360					365				
	Trp	Met	Asn	Leu	Ala	Glu	Lys	Ile	Pro	Gln	Ser	Gln	Tyr	Asp	Val	Val	
		370					375					380					
40	Ser	Asp	His	Val	Ser	Lys	Val	Thr	Phe	Phe	Asn	Leu	Asn	Glu	Thr	Lys	
	385					390					395					400	
	Pro	Arg	Gly	Lys	Phe	Thr	Tyr	Asp	Ala	Val	Tyr	Cys	Cys	Asn	Glu	His	
				405						410					415		
45	Glu	Cys	His	His	Arg	Tyr	Ala	Glu	Leu	Tyr	Val	Ile	Asp	Val	Asn	Ile	
				420					425					430			
	Asn	Ile	Ser	Cys	Glu	Thr	Asp	Gly	Tyr	Leu	Thr	Lys	Met	Thr	Cys	Arg	
50			435					440					445				
	Trp	Ser	Thr	Ser	Thr	Ile	Gln	Ser	Leu	Ala	Glu	Ser	Thr	Leu	Gln	Leu	
				450			455						460				

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	Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His	
	465	470 475 480
5	Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr	
		485 490 495
	Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp	
		500 505 510
10	Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys	
		515 520 525
	Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys	
15		530 535 540
	Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys	
		545 550 555 560
20	Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu	
		565 570 575
	Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys	
		580 585 590
25	Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala	
		595 600 605
	Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn	
30		610 615 620
	Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met	
		625 630 635 640
35	Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys	
		645 650 655
	Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser	
		660 665 670
40	Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn	
		675 680 685
	Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu	
45		690 695 700
	Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile	
		705 710 715 720
50	Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser	
		725 730 735

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Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser
 740 745 750
 5 Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met
 755 760 765
 Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys
 770 775 780
 10 Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His
 785 790 795 800
 Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met
 805 810 815
 15 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp
 820 825 830
 Ile Glu Lys His Gln Ser Asp
 20 835

(2) INFORMATION FOR SEQ ID NO:11:

25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2624 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: cDNA

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC GGTGAGTTG 60
 GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG 120
 40 TTTTGTTACA TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTC AATCCAATTA 180
 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT 240
 45 TGCCTGCTGG GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG 300
 AACCTAAGTT TAATTCAAAG GGTACTCACT TTTCTAACTT ATCCAAAACA ACTTTCCACT 360
 GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA 420
 50 AGACATTTGT TTCAACAGTA AATTCTTTAG TTTTCAACA AATAGATGCA AACTGGAACA 480
 TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA 540

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	AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT	600
5	TAGAAGATTAC ACCTCTGGTT CCCCCAAAAG GCAGTTTTCA GATGGTTCAC TGCAATTGCA	660
	GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC	720
	TCCTTATGTG TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG	780
10	TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG	840
	ATGATGGTAA TTTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTCAAT	900
15	ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC AAGATTGTCT	960
	CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA	1020
	GGGGCAAGAG ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA	1080
20	CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTGGG TCTAATGTTT	1140
	CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAAGAG ATTGTTTGGT	1200
25	GGATGAATTT AGCTGAGAAA ATTCCTCAA GCCAGTATGA TGTTGTGAGT GATCATGTTA	1260
	GCAAAGTTAC TTTTTTCAAT CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG	1320
	CAGTGTACTG CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG	1380
30	ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT	1440
	GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA	1500
35	GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC AAAGATTGCT	1560
	ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT	1620
	ACACAATGTG GATTAGGATC AATCACTCTC TAGGTTCACT TGA CTCTCCA CCAACATGTG	1680
40	TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA	1740
	TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC	1800
45	AATTCCAGAT TCGCTATGGT TTAAGTGGA AAGAAGTACA ATGGAAGATG TATGAGGTTT	1860
	ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG	1920
	TTCAGGTGCG CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG	1980
50	CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA	2040
	TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA	2100

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AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT TCCTGCAATG 2160
GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC TTCCTGTGG ACAGAGCAAG 2220
5 CACATACTGT TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT 2280
TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCCTCAGT GCTTATCCTT 2340
TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT 2400
10 ATTTTATTAT TGAGTGGAAG AATCTTAATG AAGATGGTGA AATAAAATGG CTTAGAATCT 2460
CTTCATCTGT TAAGAAGTAT TATATCCATG ATCATTTTAT CCCCATTGAG AAGTACCAGT 2520
15 TCAGTCTTTA CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA 2580
CTCAAGATGA TATTGAAAAA CACCAGAGTG ATTGATAAGG ATCC 2624

(2) INFORMATION FOR SEQ ID NO:12:

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2948 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

25

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CCATTGAAGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGGATTT CCAAAATGTC 60
35 GTAATAACCC CGCCCCGTTG ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA 120
TAAGCAGAGC TCGTTTAGTG AACCCTCAGA TCTCTAGAAG CTGGGTACCA GCTGCTAGCA 180
40 AGCTTGCTAG CGGCCGCCAG TGTGATGGAT ATCTGCAGAA TTCGGCTTTC TCTGCCTTCG 240
GTCGAGTTGG ACCCCCGGAT CAAGGTGTAC TTCTCTGAAG TAAGATGATT TGTCAAAAAT 300
TCTGTGTGGT TTTGTTACAT TGGGAATTTA TTTATGTGAT AACTGCGTTT AACTTGTCAT 360
45 ATCCAATTAC TCCTTGGAGA TTTAAGTTGT CTTGCATGCC ACCAAATTC AACTATGACT 420
ACTTCCTTTT GCCTGCTGGG CTCTCAAAGA AACTTCAAA TTCGAATGGA CATTATGAGA 480
50 CAGCTGTTGA ACCTAAGTTT AATTCAAGTG GTACTCACTT TTCTAACTTA TCCAAAACAA 540
CTTCCACTG TTGCTTTCGG AGTGAGCAAG ATAGAACTG CTCCTTATGT GCAGACAACA 600

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	TTGAAGGAAA GACATTTGTT TCAACAGTAA ATTCTTTAGT TTTTCAACAA ATAGATGCAA	660
	ACTGGAACAT ACAGTGCTGG CTAAAAGGAG ACTTAAAATT ATTCATCTGT TATGTGGAGT	720
5	CATTATTTAA GAATCTATTG AGGAATTATA ACTATAAGGT CCATCTTTTA TATGTTCTGC	780
	CTGAAGTGTT AGAAGATTCA CCTCTGGTTC CCCAAAAGG CAGTTTTTCAG ATGGTTCACT	840
10	GCAATTGCAG TGTTACAGAA TGTTGTGAAT GTCTTGTGCC TGTGCCAACA GCCAAACTCA	900
	ACGACACTCT CCTTATGTGT TTGAAAATCA CATCTGGTGG AGTAATTTTC CAGTCACCTC	960
	TAATGTCAGT TCAGCCCATATA AATATGGTGA AGCCTGATCC ACCATTAGGT TTGCATATGG	1020
15	AAATCACAGA TGATGGTAAT TTAAAGATTT CTTGGTCCAG CCCACCATTG GTACCATTTC	1080
	CACTTCAATA TCAAGTGAAA TATTCAGAGA ATTCTACAAC AGTTATCAGA GAAGCTGACA	1140
20	AGATTGTCTC AGCTACATCC CTGCTAGTAG ACAGTATACT TCCTGGGTCT TCGTATGAGG	1200
	TTCAGGTGAG GGGCAAGAGA CTGGATGGCC CAGGAATCTG GAGTGACTGG AGTACTCCTC	1260
	GTGTCTTTAC CACACAAGAT GTCATATACT TTCCACCTAA AATTCTGACA AGTGTGGGT	1320
25	CTAATGTTTC TTTTCACTGC ATCTATAAGA AGGAAAACAA GATTGTTCCC TCAAAAGAGA	1380
	TTGTTTGGTG GATGAATTTA GCTGAGAAAA TTCCTCAAAG CCAGTATGAT GTTGTGAGTG	1440
30	ATCATGTTAG CAAAGTTACT TTTTCAATC TGAATGAAAC CAAACCTCGA GGAAAGTTTA	1500
	CCTATGATGC AGTGTACTGC TGCAATGAAC ATGAATGCCA TCATCGCTAT GCTGAATTAT	1560
	ATGTGATTGA TGTCAATATC AATATCTCAT GTGAACTGA TGGGTACTTA ACTAAAATGA	1620
35	CTTGCAGATG GTCAACCAGT ACAATCCAGT CACTTGCGGA AAGCACTTTG CAATTGAGGT	1680
	ATCATAGGAG CAGCCTTTAC TGTTCTGATA TTCCATCTAT TCATCCCATA TCTGAGCCCA	1740
40	AAGATTGCTA TTTGCAGAGT GATGGTTTTT ATGAATGCAT TTTCCAGCCA ATCTTCCTAT	1800
	TATCTGGCTA CACAATGTGG ATTAGGATCA ATCACTCTCT AGGTTCACTT GACTCTCCAC	1860
	CAACATGTGT CCTTCCTGAT TCTGTGGTGA AGCCACTGCC TCCATCCAGT GTGAAAGCAG	1920
45	AAATTACTAT AAACATTGGA TTATTGAAAA TATCTTGGGA AAAGCCAGTC TTTCCAGAGA	1980
	ATAACCTTCA ATTCCAGATT CGCTATGGTT TAAGTGGAAG AGAAGTACAA TGGAAGATGT	2040
50	ATGAGGTTTA TGATGCAAAA TCAAAATCTG TCAGTCTCCC AGTTCCAGAC TTGTGTGCAG	2100
	TCTATGCTGT TCAGGTGCGC TGTAAGAGGC TAGATGGACT GGGATATTGG AGTAATTGGA	2160
	GCAATCCAGC CTACACAGTT GTCATGGATA TAAAAGTTCC TATGAGAGGA CCTGAATTTT	2220

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5 GGAGAATAAT TAATGGAGAT ACTATGAAAA AGGAGAAAAA TGTCACTTTA CTTTGGAAGC 2280
 CCCTGATGAA AAATGACTCA TTGTGCAGTG TTCAGAGATA TGTGATAAAC CATCATACTT 2340
 CCTGCAATGG AACATGGTCA GAAGATGTGG GAAATCACAC GAAATTCAC TCCCTGTGGA 2400
 CAGAGCAAGC ACATACTGTT ACGGTTCTGG CCATCAATTC AATTGGTGCT TCTGTTGCAA 2460
 10 ATTTTAATTT AACCTTTTCA TGGCCTATGA GCAAAGTAAA TATCGTGCAG TCACTCAGTG 2520
 CTTATCCTTT AAACAGCAGT TGTGTGATTG TTCCTGGAT ACTATCACCC AGTGATTACA 2580
 AGCTAATGTA TTTTATTATT GAGTGGAAAA ATCTTAATGA AGATGGTGAA ATAAAATGGC 2640
 15 TTAGAATCTC TTCATCTGTT AAGAAGTATT ATATCCATGA TCATTTTATC CCCATTGAGA 2700
 AGTACCAGTT CAGTCTTTAC CCAATATTTA TGGAAGGAGT GGGAAAACCA AAGATAATTA 2760
 20 ATAGTTTCAC TCAAGATGAT ATTGAAAAAC ACCAGAGTGA TGCAGGTGAC TACAAGGACG 2820
 ACGATGACAA GTAGGGATCC AGACATGATA AGATACATTG ATGAGTTTGG ACAACCCACA 2880
 ACTAGAATGC AGTGAAAAAA ATGCTTTATT TGTGAAATTT GTGATGCTAT TGCTTTATTT 2940
 25 GTAACCAT 2948

(2) INFORMATION FOR SEQ ID NO:13:

30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 804 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: protein

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

45 Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile
 1 5 10 15
 Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg
 20 25 30
 50 Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu
 35 40 45
 Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr
 50 55 60

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	Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser	
	65	70 75 80
5	Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp	
		85 90 95
	Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val	
		100 105 110
10	Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn	
		115 120 125
	Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val	
15		130 135 140
	Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His	
		145 150 155 160
20	Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro	
		165 170 175
	Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu	
		180 185 190
25	Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr	
		195 200 205
	Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser	
30		210 215 220
	Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro	
		225 230 235 240
35	Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser	
		245 250 255
	Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys	
		260 265 270
40	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	
		275 280 285
	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	
45		290 295 300
	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	
		305 310 315 320
50	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	
		325 330 335

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Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys
 340 345 350
 5 Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp
 355 360 365
 Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val
 370 375 380
 10 Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys
 385 390 395 400
 Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His
 405 410 415
 15 Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile
 420 425 430
 Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg
 435 440 445
 20 Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu
 450 455 460
 25 Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His
 465 470 475 480
 Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr
 485 490 495
 30 Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp
 500 505 510
 Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys
 515 520 525
 35 Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys
 530 535 540
 40 Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys
 545 550 555 560
 Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu
 565 570 575
 45 Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys
 580 585 590
 50 Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala
 595 600 605
 Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn
 610 615 620

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Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met
 625 630 635 640
 5 Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys
 645 650 655
 Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser
 660 665 670
 10 Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn
 675 680 685
 Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu
 690 695 700
 15 Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile
 705 710 715 720
 20 Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser
 725 730 735
 Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser
 740 745 750
 25 Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met
 755 760 765
 Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys
 770 775 780
 30 Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Gly Lys
 785 790 795 800
 35 Phe Thr Ile Leu

(2) INFORMATION FOR SEQ ID NO:14:

- 40 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2507 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 45 (ii) MOLECULE TYPE: cDNA
 50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

	GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC GGTCGAGTTG	60
5	GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG	120
	TTTTGTTACA TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA	180
10	CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT	240
	TGCCTGCTGG GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG	300
	AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA ACTTTCCACT	360
15	GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA	420
	AGACATTTGT TTCAACAGTA AATTCTTTAG TTTTCAACA AATAGATGCA AACTGGAACA	480
20	TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA	540
	AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT	600
	TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTTCA GATGGTTCAC TGCAATTGCA	660
25	GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC	720
	TCCTTATGTG TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG	780
30	TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG	840
	ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTTCAAT	900
	ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC AAGATTGTCT	960
35	CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA	1020
	GGGGCAAGAG ACTGGATGGC CCAGGAATCT GGAGTGAAGT GAGTACTCCT CGTGTCTTTA	1080
40	CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTGGG TCTAATGTTT	1140
	CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAGAG ATTGTTTGGT	1200
	GGATGAATTT AGCTGAGAAA ATTCCTCAAA GCCAGTATGA TGTGTGAGT GATCATGTTA	1260
45	GCAAAGTTAC TTTTTTCAAT CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG	1320
	CAGTGTACTG CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG	1380
50	ATGTCAATAT CAATATCTCA TGTGAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT	1440
	GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA	1500
	GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC AAAGATTGCT	1560

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ATTTCAGAG TGATGGTTTT TATGAATGCA TTTTCAGCC AATCTTCCTA TTATCTGGCT 1620
ACACAATGTG GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG 1680
5 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA 1740
TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCAGAG AATAACCTTC 1800
10 AATTCCAGAT TCGCTATGGT TTAAGTGGAA AAGAAGTACA ATGGAAGATG TATGAGGTTT 1860
ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG 1920
TTCAGGTGCG CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG 1980
15 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA 2040
TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA 2100
20 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT TCCTGCAATG 2160
GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG 2220
CACATACTGT TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT 2280
25 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT GCTTATCCTT 2340
TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT 2400
30 ATTTTATTAT TGAGTGGAAA AATCTTAATG AAGATGGTGA AATAAAATGG CTTAGAATCT 2460
CTTCATCTGT TAAGAAGTAT TATATCCATG GTAAGTTTAC TATACTT 2507

(2) INFORMATION FOR SEQ ID NO:15:

35

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
40 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

45

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

50

GTAAGTTATT TGNNNNNATA TCCTAACAG

29

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(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GTAAGCATTG GCNNNNNTTT TAAATTCAG

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GTAAGTACCA AANNNNNTTT TCAATATAG

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GTAAGTTATG CANNNNNTTT TTCCTTAAG

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(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GTAAGTATAT TTNNNNAATA TTAAACAG

28

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GTAGGTTATG TANNNNNCCC TCATTACAG

29

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GTAAGAAAAC AGNNNNNTGT TTCAAATAG

29

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(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

15 GTACGTATTA TTNNNNNTAT CTTTAAAG 29

(2) INFORMATION FOR SEQ ID NO:23:

- 20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: cDNA

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTATGTCAAG CTNNNNNAAA AATTCTAG 29

35 (2) INFORMATION FOR SEQ ID NO:24:

- 40 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

50 GTACCTTTTA CTNNNNNCTT ATTTTACAG 29

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(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GTCTGCAGAG ATNNNNNGTC ATTTTGCAG

29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GTATTCCCAA TTNNNNNTAT TTACTACAG

29

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GTATTCCCAA TTNNNNNTAT TTACTACAG

29

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(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GTAAGTTTAC TANNNNNTTT TCTCCTCAG

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GTAAAAATTA TANNNNNTTT CTTTTTCAG

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GTATTGTACT TGNNNNNTAT CCTTTGTAG

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(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GTGCTTTTT CANNNNNTTA TCTAAACAG

29

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GTACATTGT CTNNNNNCTT TTCTTTTAG

29

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GTATCCAGTG TTNNNNNCTT TTAAACAG

29

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CLAIMS

1. An OB receptor protein preparation
5 containing an OB receptor protein, optionally in a
pharmaceutically acceptable formulation, said OB
receptor protein having part or all of the amino acid
sequence according to Seq. ID No. 1 and one or more of
the biological properties of naturally occurring OB
10 receptor protein.
2. An OB receptor protein preparation
containing an OB receptor protein, optionally in a
pharmaceutically acceptable formulation, wherein said OB
15 receptor protein amino acid sequence is selected from
among amino acid sequences (according to Seq. ID No. 1):
 - (a) 1-896;
 - (b) 22-896 optionally with an N-terminal
methionyl residue;
 - 20 (c) 23-896 optionally with an N-terminal
methionyl residue;
 - (d) 29-896 optionally with an N-terminal
methionyl residue;
 - (e) 1-839;
 - 25 (f) 22-839 optionally with an N-terminal
methionyl residue;
 - (g) 29-839 optionally with an N-terminal
methionyl residue;
 - (h) 1-841;
 - 30 (i) 22-841 optionally with an N-terminal
methionyl residue;
 - (j) 23-841 optionally with an N-terminal
methionyl residue;
 - (k) 29-841 optionally with an N-terminal
35 methionyl residue;
 - (l) 1-891;

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(m) 22-891 optionally with an N-terminal methionyl residue;

(n) 23-891 optionally with an N-terminal methionyl residue;

5 (o) 29-891 optionally with an N-terminal methionyl residue;

(p) of subparts (l) through (o) further having the C-terminal amino acids, beginning at position 892, of OB receptor B (Seq. ID No. 3) or C (Seq. ID No. 5); and,

10 (q) a chemically modified derivative of any of subparts (a) through (p).

3. An OB receptor protein preparation of claim 2 wherein said OB receptor protein is further selected from among the OB receptor proteins of subparts (l) through (o) further having the C-terminal amino acids, beginning at position 892, of OB receptor protein D (Seq. ID No. 7).

20

4. An OB receptor protein preparation of claim 2 wherein said OB receptor protein is further selected from among the OB receptor proteins of subparts (l) through (o) further having substituted the C-terminal amino acids, beginning at position 799, G K F T I L (Seq. ID No. 13).

25

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5. An OB receptor protein preparation according to any of claims 1 through 4, wherein the extracellular domain of said OB receptor protein is modified, said modification selected from among:

- (a) deletion of all or part of the random coil domain;
- (b) modification of one or both "WSXWS" boxes by substitution of the first serine with another amino acid;
- (c) modification of one or both "WSXWS" boxes by substitution of the last serine with another amino acid; and
- (d) modification of one or both "WSXWS" boxes by substitution of the first tryptophan with another amino acid.

6. A DNA molecule encoding an OB receptor protein according to any of claims 1-5 selected from the group consisting of:

- (a) the DNA sequences set forth in Seq. ID nos. 2, 4, 6, 8, 11, 12, and 14;
- (b) a DNA which selectively hybridizes to a DNA of subpart (a); and
- (c) a DNA which, but for the degeneracy of the genetic code would hybridize to a DNA of subpart (a) or (b).

7. A biologically functional viral or plasmid vector containing a DNA of claim 6.

8. A procaryotic or eucaryotic host cell containing the vector of claim 7.

9. A host cell modified so that expression of endogenous OB receptor protein is enhanced.

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10. A host cell of claim 9 which is an isolated human host cell.

5 11. A process for producing an OB receptor protein comprised of culturing, under suitable conditions, a host cell according to any of claims 8, 9 or 10, obtaining the OB receptor produced, and optionally preparing a pharmaceutical composition
10 containing said OB receptor.

 12. A method of treating an individual for a therapeutic disorder selected from among obesity, diabetes, high blood lipid levels, and high cholesterol
15 levels comprised of administering a therapeutic amount of an OB receptor protein preparation containing an OB receptor protein according to any of claims 1-5, or produced by the process according to claim 11.

20 13. A method of treating an individual for weight loss or weight maintenance for solely cosmetic purposes comprised of administering an effective amount of an OB receptor preparation containing an OB receptor protein according to any of claims 1-5, or produced by
25 the process according to claim 11.

 14. Use of an OB receptor protein according to claims 1-5, or produced by the process of claim 11, for manufacturing a medicament for the treatment of
30 obesity, diabetes, high blood lipid levels, or high cholesterol levels.

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15. An OB protein/OB receptor protein complex preparation, containing an OB protein moiety and an OB receptor protein moiety, optionally in a pharmaceuti-
5 cally acceptable formulation, wherein:

(a) said OB receptor protein is selected from among those set forth in any of claims 1 and 2;

(b) said OB protein moiety is selected
10 from among:

(i) a naturally occurring OB protein; and,

(ii) a non-naturally occurring OB protein, analog or derivative thereof.

15

16. An OB protein/OB receptor protein complex preparation of claim 15 wherein said OB receptor protein is selected from among those set forth in any of claims 3, 4, and 5.

20

17. A method of treating an individual for a therapeutic disorder selected from among obesity, diabetes, high blood lipid levels, and high cholesterol levels comprised of administering a therapeutic amount
25 of an OB protein/OB receptor protein complex preparation of claims 15 or 16.

18. A method of claim 17 wherein said OB protein/OB receptor protein complex preparation is
30 formed in vivo by administering, into a patient, a first population of cells expressing an OB protein, and a second population of cells expressing an OB receptor protein.

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19. A method of treating an individual for weight loss or weight maintenance for solely cosmetic purposes comprised of administering a therapeutic amount of an OB protein/OB receptor protein complex preparation containing an OB receptor protein moiety according to any of claims 1-5, or produced by the process according to claim 11.
20. Use of an OB protein/OB receptor protein complex preparation, according to claims 15 or 16, for manufacturing a medicament for the treatment of obesity, diabetes, high blood lipid levels, or high cholesterol levels.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00128

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N5/10 C07K14/715 C07K16/28 C12Q1/68
G01N33/50 A61K38/17 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL, vol. 83, 29 December 1995, pages 1263-1271, XP000602068 TARTAGLIA, L.A., ET AL. : "IDENTIFICATION AND EXPRESSION CLONING OF A LEPTIN RECEPTOR, OB-R" see the whole document & EMBL SEQUENCE DATA LIBRARY, 30 December 1995, TARTAGLIA, L.A., ET AL. : "IDENTIFICATION AND EXPRESSION CLONING OF A LEPTIN RECEPTOR, OB-R" ACCESSION No. U43168	1,3,6-8
P,X	WO 96 08510 A (PROGENITOR INC) 21 March 1996 see the whole document --- -/-	1,2,6-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

28 April 1997

Date of mailing of the international search report

07. 05. 97

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>NATURE MEDICINE, vol. 2, no. 5, May 1996, pages 585-589, XP0002019361 CIOFFI, J.A., ET AL . : "NOVEL B219/OB RECEPTOR ISOFORMS: POSSIBLE ROLE OF LEPTIN IN HEMATOPOIESIS AND REPRODUCTION" see the whole document & EMBL SEQUENCE DATA LIBRARY, 26 April 1996, HEIDELBERG, GERMANY, CIOFFI, J.A., ET AL . : "NOVEL B219/OB ISOFORMS: POSSIBLE ROLE OF LEPTIN IN HEMATOPOIESIS AND REPRODUCTION" ACCESSION No.s U52912, U52913; U52914 ---</p>	1,2,6-8
P,X	<p>CURRENT BIOLOGY, vol. 6, no. 9, 1 September 1996, pages 1170-1180, XP000673008 BENNETT, B.D., ET AL.: "A ROLE FOR LEPTIN AND ITS COGNATE RECEPTOR IN HEMATOPOIESIS" see the whole document & EMBL SEQUENCE DATA LIBRARY, 7 September 1996, HEIDELBERG, GERMANY, BENNETT, B.D., ET AL . : "A ROLE FOR LEPTIN AND ITS COGNATE RECEPTOR IN HEMATOPOIESIS" ACCESSION No. U66496 ---</p>	1-3,6-8
P,X	<p>BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 224, no. 2, 16 July 1996, pages 597-604, XP002029745 IIDA, M., ET AL . : "SUBSTITUTION AT CODON 269 (GLUTAMINE - PROLIN) OF THE LEPTIN RECEPTOR (OB-R) cDNA IS THE ONLY MUTATION FOUND IN THE ZUCKER FATTY (fa/fa) RAT" see the whole document & EMBL SEQUENCE DATA LIBRARY, 12 June 1996, HEIDELBERG, GERMANY, IIDA, M., ET AL . : "PHENOTYPE-LINKED AMINO-ACID ALTERATION IN LEPTIN RECEPTOR cDNA FROM ZUCKER FATTY (fa/fa) RAT" ACCESSION No. D84125 --- -/--</p>	1,6-8

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>CELL, vol. 84, 9 February 1996, pages 491-495, XP002029746 CHEN, H., ET AL . : "EVIDENCE THAT THE DIABETES GENE ENCODES THE LEPTIN RECEPTOR: IDENTIFICATION OF A MUTATION IN THE LEPTIN RECEPTOR GENE IN db/db MICE" see the whole document & EMBL SEQUENCE DATA LIBRARY, 11 February 1996, HEIDELBERG, GERMANY, CHEN,H., ET AL . : "EVIDENCE THAT THE DIABETES GENE ENCODES THE LEPTIN RECEPTOR: IDENTIFICATION OF A MUTATION IN THE LEPTIN RECEPTOR GENE IN db/db MICE" ACCESSION No. U46135 -----</p>	1,6-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application

PCT/US 97/0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608510 A	21-03-96	AU 3419495 A	29-03-96
		CA 2176463 A	21-03-96
		EP 0730606 A	11-09-96
